NATIONAL AGRICULTURAL LIBRARY ARCHIVED FILE

Archived files are provided for reference purposes only. This file was current when produced, but is no longer maintained and may now be outdated. Content may not appear in full or in its original format. All links external to the document have been deactivated. For additional information, see http://pubs.nal.usda.gov.

Information Resources on Canine Models in Biomedical Research, 1990-2009

United States Department of Agriculture

Agricultural Research Service

National Agricultural Library

Animal Welfare Information Center

August 2009

Information Resources on Canine Models in Biomedical Research, 1990-2009

August 2009

United States Department of Agriculture | Agricultural Research Service | National Agricultural Library | Animal Welfare Information Center

Compiled by:

Cynthia P. Smith, M.S.
Animal Welfare Information Center
National Agricultural Library
U.S. Department of Agriculture
Beltsville, Maryland 20705
E-mail: awic@ars.usda.gov
Web site: http://awic.nal.usda.gov

Published in cooperation with the **Virginia-Maryland Regional College of Veterinary Medicine**
http://www.vetmed.vt.edu/Organization/Maryland/

Available online at: http://www.nal.usda.gov/awic/pubs/DogModels/models.shtml

Disclaimers

The U.S. Department of Agriculture (USDA) prohibits discrimination in all its programs and activities on the basis of race, color, national origin, age, disability, and where applicable, sex, marital status, familial status, parental status, religion, sexual orientation, genetic information, political beliefs, reprisal, or because all or a part of an individual's income is derived from any public assistance program. (Not all prohibited bases apply to all programs.) Persons with disabilities who require alternative means for communication of program information (Braille, large print, audiotape, etc.) should contact USDA's TARGET Center at (202) 720-2600 (voice and TDD). To file a complaint of discrimination write to USDA, Director, Office of Civil Rights, 1400 Independence Avenue, S.W., Washington, D.C. 20250-9410 or call (800) 795-3272 (voice) or (202) 720-6382 (TDD). USDA is an equal opportunity provider and employer.

The use of trade, firm, or corporation names in this publication (or page) is for the information and convenience of the reader. Such use does not constitute an official endorsement or approval by the United States Department of Agriculture or the Agricultural Research Service of any product or service to the exclusion of others that may be suitable.

Materials appearing in this publication do not necessarily represent positions or policies of the U.S. Department of Agriculture or any agencies thereof.

Table of Contents

About this Document iii

Bibliography

Aging Models 1
Cardiovascular System 9
Dental and Oral 133
Digestive System 155
Endocrine System 181
Hemodynamics 193
Immune System 215
Molecular Genetics 235
Musculoskeletal System 249
Nervous System 285
Oncology 315
Pharmacology 331
Reproductive System 403
Respiratory System 407
Sensory Organs 441
Toxicology 451
Urinary System 471

The Animal Welfare Information Center (AWIC) is part of the National Agricultural Library, which is located in Beltsville, Maryland. Established in 1986 as mandated by amendments to the Animal Welfare Act, AWIC provides information for improved animal care and use in research, teaching, and testing.
http://awic.nal.usda.gov

About this Document

This document is an adjunct resource to the previously published Information Resources on the Care and Welfare of Dogs, March 2008 publication. That document is available online at http://www.nal.usda.gov/awic/pubs/Dogs/dogs.shtml.

It is intended for basic researchers, biomedical researchers, veterinarians, and technicians, that wish to explore the scientific published literature on canines used as models of human disease, testing of new medical technologies, drug screening, and basic science discovery. It is not meant to be all inclusive but to touch on a variety of research areas that the canine has played as an important large animal model.

Citations have been s subcategorized into groupings related to major body systems and specific areas of research for easier browsing. Citations included in these chapters were published between 1990 and February 2009 and they were selected from multiple sources. In each chapter, the citations are arranged alphabetically according to the last name of the primary author.

Each citation in the bibliography contains descriptor terms, an abstract when available, and the NAL call number if the particular source is available at the National Agricultural Library (NAL). Information on how to request materials that are included in the collection of the National Agricultural Library (NAL) may be found on the Request Library Materials page. Please read carefully as there are certain restrictions on media and document types. All patrons are encouraged to explore local library resources first before contacting the National Agricultural Library.

For online resources related to the care of dogs in research, visit the AWIC web site: http://awic.nal.usda.gov and click on Research Animals, Laboratory Animal Species.

National Agricultural Library Document Delivery
Information on how to request materials that are included in the collection of the National Agricultural Library (NAL) may be found on the the Request Library Materials page at http://www.nal.usda.gov/services/request.shtml. Please read carefully as there are certain restrictions on media and document types. All patrons are encouraged to explore local library resources first before contacting the National Agricultural Library.

Acknowledgements
The author wishes to acknowledge Kristina Adams and Sandra Ball for their participation in the final editing and conversion process of this document. Their support is greatly appreciated.

Aging Models

Araujo, J.A., A.D.F. Chan, L.L. Winka, P.A. Seymour, and N.W. Milgram (2004). **Dose-specific effects of scopolamine on canine cognition: impairment of visuospatial memory, but not visuospatial discrimination**. *Psychopharmacology* 175(1): 92-98. ISSN: 0033-3158.
Abstract: Rationale. The cholinergic system is linked extensively to memory, but its exact role remains controversial. In particular, scopolamine-induced impairment in rodents is not task specific, which may be due to difficulty in developing rodent protocols to assess deficits in recent memory, in which the remembered event is brief and distinct, and/or to non-specific behavioral impairment. Objectives. The present study sought to determine whether scopolamine-induced deficits in recent memory, using a working memory task, could be dose-specifically dissociated from deficits in associative memory in dogs. Methods. A Latin-square design was used to determine the effect of scopolamine (5, 10 and 15 mug/kg; SC) on a variable delayed-non-matching-to-position (DNMP) task, which assesses visuospatial working memory. Subsequently, the minimal effective dose (15 mug/kg; SC) was administered prior to testing on a landmark discrimination task, which provides a measure of allocentric spatial ability, a black-white discrimination task, an oddity discrimination task and tests of exploratory behavior. We also investigated the effects of a 30 mug/kg dose (SC) on tests of oddity discrimination and behavioral activity. Results. A 15 mug/kg dose produced significant impairment on the DNMP task, but did not affect performance of any discrimination task and did not alter behavior on tests of open field or curiosity. A 30 mug/kg dose caused disruption on discrimination performance and on open field measures. Conclusions. Working memory performance is most sensitive to scopolamine-induced impairment and can be dissociated from scopolamine-induced deficits in discrimination performance and non-cognitive behaviors. The present results indicate that scopolamine-induced impairments of working memory in the dog can serve as a model of age-related cholinergic dysfunction.
Descriptors: aging, behavior, nervous system, neural coordination, pharmacology, age related cholinergic dysfunction, visuospatial discrimination, visuospatial memory, impairment.

Colle, M.A., C. Duyckaerts, T. Uchihara, F. Dessi, F. Crespeau, D. Seilhan, and J.J. Hauw (1997). **Behavioral alterations and beta-amyloid accumulation in aged canine brain**. *Society for Neuroscience Abstracts* 23(1-2): 1639 ISSN: 0190-5295.
NAL Call Number: QP351.S6
Descriptors: aging, behavior, metabolism, nervous system, neural coordination, aged, aged canine brain accumulation, animal model, behavior, behavioral alterations, beta amyloid.

Colle, M.A., J.J. Hauw, F. Crespeau, T. Uchihara, H. Akiyama, F. Checler, P. Pageat, and C. Duykaerts (2000). **Vascular and parenchymal abeta deposition in the aging dog: correlation with behavior**. *Neurobiology of Aging* 21(5): 695-704. ISSN: 0197-4580.
Abstract: The behavior of 25 dogs was indirectly assessed by a formal questionnaire (evaluation of Age-Related Cognitive and Affective Disorders-ARCAD), filled out by the owner.

The density of diffuse and vascular deposits was evaluated using four anti-Abeta peptide antibodies, in four temporal areas. Parenchymal, diffuse deposits of Abeta42 peptide were found in all aged animals but one. They were Congo red negative and were not immunostained by the anti-Abeta40 antibody, contrary to the vascular deposits. The densities of vascular and parenchymal deposits were not correlated. The ARCAD score was correlated with age, density of Abeta parenchymal and vascular deposits, and with the number of areas containing deposits (extension index). Multivariate analysis showed that the age and the extension index explained most of the variance. Congo red positivity (indicating that the Abeta peptide has the characteristics of an amyloid substance) is limited in the dog to the vascular wall and is associated, as in man, with the deposition of the Abeta 1-40 isoform. Parenchymal Abeta deposition seems to be a common correlate of behavioral problems in aging dogs.
Descriptors: aging, behavior, biochemistry and molecular biophysics, neural coordination, Alzheimer's disease, behavioral and mental disorders, nervous system disease, canine model, senile plaques, animal model, age related cognitive and affective disorders questionnaire, arcad questionnaire, analytical method, cognitive disturbances, cognitive evaluation.

Cooley, D.M., D.L. Schlittler, L.T. Glickman, M. Hayek, and D.J. Waters (2003). **Exceptional longevity in pet dogs is accompanied by cancer resistance and delayed onset of major diseases.** *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 58(12): B1078-84. ISSN: 1079-5006.
Abstract: To characterize extreme aged pet dogs as a first step in developing an animal model of exceptional longevity, we constructed lifetime medical histories for 345 Rottweiler dogs using information collected from owners and veterinarians. Extreme aged dogs (alive at the 95th percentile age at death for the study population, > or =13.3 years) were compared with a usual longevity group (9-10 years). Exceptional longevity in Rottweiler dogs was accompanied by a significant delay in the onset of major life-threatening diseases; 76% of extreme aged dogs remained free of all major diseases during the first 9 years of life. Only 19% of extreme aged dogs died of cancer versus 82% of dogs with usual longevity (p <.0001). The reduction in cancer mortality in oldest-old pet dogs mimics that seen in human centenarians and provides strong rationale for using this animal model to study comparative mechanisms of cancer resistance in the extreme aged.
Descriptors: animal model, longevity, aging, medical history, cancer resistance.

Head, E., J. Liu, B.N. Ames, B.A. Muggenburg, N.W. Milgram, and C.W. Cotman (2000). **Oxidative stress, beta-amyloid and cognitive function in the aged canine brain**. *Society for Neuroscience Abstracts* 26(1 2): Abstract No. 873.2 ISSN: 0190-5295.
NAL Call Number: QP351.S6
Abstract: Several studies report evidence of oxidative stress in aged human brain. We examined the extent of lipid peroxidation in the aged canine, which we have suggested as a model of human brain aging. Eighteen beagle dogs ranging in age from 2-15 years were tested for size discrimination learning and subsequently the extent of beta-amyloid-42 (Abeta) deposition was measured in the prefrontal cortex using immunostained 4% paraformaldehyde-fixed sections. Oxidative damage to lipids was measured in serum and in frozen blocks from the contralateral prefrontal cortex using a biochemical assay for malondialdehyde (MDA) and

GC-MS methodology. MDA levels were significantly elevated with age (F(1,17)=12.144 p<.003). In addition, MDA levels were a significant predictor of Abeta deposition in the prefrontal cortex (r=.70 p<.001, n=13) even when the effects of age were partialled out (r=.5041, p<.039 n=13). Further, MDA levels were significantly correlated with cognitive function; higher error scores were associated with increased levels of MDA (r=.534 p<.04). Finally, serum levels of MDA predicted brain levels of MDA (r=.494 p<.037) and thus serum assays may serve as a measure of brain oxidative stress. These results suggest that like the human, dogs show evidence of oxidative stress in the brain that is associated with age, the extent of Abeta deposition and with cognitive function.
Descriptors: aging, nervous system, neural coordination, gc ms, gas chromatography mass spectrometry, analytical method, biochemical assay, analytical method, cognitive function, oxidative stress, meeting abstract.

Milgram, N.W. (2003). **Cognitive experience and its effect on age dependent cognitive decline in beagle dogs**. *Neurochemical Research* 28(11): 1677-1682. ISSN: 0364-3190.
NAL Call Number: QP356.3 .N457
Abstract: Test-sophisticated beagle dogs show marked age sensitivity in a size discrimination learning task, with old and senior dogs performing significantly more poorly than young dogs. By contrast, age differences in learning were not seen in dogs naive with respect to neuropsychological test experience. These results indicate that old animals benefit less from prior cognitive experience than young animals, which is an example of an age-dependent loss in plasticity. This finding also suggests that behaviorally experienced animals are a more useful model of human cognitive aging than behaviorally naive animals. We also looked at the effect of a program of behavioral enrichment in aged dogs. One year of enrichment did not lead to significant differences, but after 2 years the behaviorally enriched group performed significantly better than the control group. The effect after 2 years indicates that a prolonged program of cognitive enrichment can serve as an effective intervention in aged dogs. These findings demonstrate that cognitive abilities in aged animals can be modified by providing behavioral experience, indicating that cognitive abilities remain moderately plastic, even in very old animals.
Descriptors: beagle, breed, age effects, cognition, neuropsychological tests, age-dependent loss in plasticity, behavioral enrichment, length of enrichment program.

Milgram, N.W., E. Head, S.C. Zicker, C.J. Ikeda Douglas, H. Murphey, B. Muggenburg, C. Siwak, D. Tapp, and C.W. Cotman (2005). **Learning ability in aged beagle dogs is preserved by behavioral enrichment and dietary fortification: a two-year longitudinal study**. *Neurobiology of Aging* 26(1): 77-90. ISSN: 0197-4580.
Abstract: The effectiveness of two interventions, dietary fortification with antioxidants and a program of behavioral enrichment, was assessed in a longitudinal study of cognitive aging in beagle dogs. A baseline protocol of cognitive testing was used to select four cognitively equivalent groups: control food-control experience (C-C), control food-enriched experience (C-E), antioxidant fortified food-control experience (A-C), and antioxidant fortified food-enriched experience(A-E). We also included two groups of young behaviorally enriched dogs, one receiving the control food and the other the fortified food. Discrimination learning and

reversal was assessed after one year of treatment with a size discrimination task, and again after two years with a black/white discrimination task. The four aged groups were comparable at baseline. At one and two years, the aged combined treatment group showed more accurate learning than the other aged groups. Discrimination learning was significantly improved by behavioral enrichment. Reversal learning was improved by both behavioral enrichment and dietary fortification. By contrast, the fortified food had no effect on the young dogs. These results suggest that behavioral enrichment or dietary fortification with antioxidants over a long-duration can slow age-dependent cognitive decline, and that the two treatments together are more effective than either alone in older dogs.
Descriptors: dietary fortification, antioxidants, longitudinal study, cognitive aging, behavioral enrichment, age-dependent cognitive decline.

Pomeroy, M.J. and J.L. Robertson (2004). **The relationship of age, sex, and glomerular location to the development of spontaneous lesions in the canine kidney: analysis of a life-span study**. *Toxicologic Pathology* 32(2): 237-242. ISSN: 0192-6233.
Abstract: It is well documented that the presence of spontaneous renal disease and renal dysfunction increases with age in many species of mammals. Such alterations in renal structure and function may significantly affect the interpretation of long-term toxicology studies. The purpose of the present study was to assess the temporal evolution of selected renal lesions (cysts, interstitial inflammation, interstitial fibrosis, and glomerulosclerosis) in laboratory Beagle dogs, an important animal model in chronic toxicology studies. We examined representative sections of the kidneys from 159 purpose-bred and laboratory housed Beagle dogs and analyzed the extent and distribution of spontaneous lesions using the World Health Organization classification system for renal lesions. All dogs examined had renal lesions of varying severities. In the youngest dogs (up to 2 years of age), the density and severity of lesions were minimal, but were more severe by middle age (defined as 3-7 years). The density and severity of interstitial fibrosis and inflammation progressed with advancing age ($p<0.0001$ for both) in both sexes. The density of tubular cysts increased linearly with advancing age in females ($p=0.0006$), but not in males ($p=0.49$). The cortical distribution of glomeruli and advancing age of dogs were significantly related to the development of glomerulosclerosis. As age increased, the presence of glomerulosclerosis increased ($p=0.0008$). These data indicate that the development of renal lesions is progressive over the lifetime of a genetically similar population of laboratory Beagle dogs maintained under optimal standard environmental conditions. This information may be useful in the interpretation of compound effects during chronic toxicology studies in the dog.
Descriptors: breed, Beagle, age differences, aging, cysts pathological, fibrosis, glomerulus, inflammation, kidney diseases, lifespan, sex differences.

Siwak, C.T., P. Gruet, F. Woehrle, B.A. Muggenburg, H.L. Murphey, and N.W. Milgram (2000). **Comparison of the effects of adrafinil, propentofylline, and nicergoline on behavior in aged dogs.** *American Journal of Veterinary Research* 61(11): 1410-1414. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Descriptors: dogs, age differences, animal behavior, efficacy, mental disorders, drug therapy, quality of life, movement, dosage, pharmacodynamics.

Siwak, C.T., P.D. Tapp, H.J. Lee, and N.W. Milgram (2000). **Age-associated changes in noncognitive behaviors in a canine model of aging**. *Society for Neuroscience Abstracts* 26(1-2): Abstract No. 873.3. ISSN: 0190-5295.

NAL Call Number: QP351.S6

Abstract: Locomotor activity and exploration, which depend on the brain's motor system, are typically viewed independently from cognition. While this may be justified in the case of locomotion, exploration involves sensory processing, investigation, responding to novel stimuli, and information gathering - all of which depend on cognitive processes. To better understand cognitive changes associated with aging, we have developed a number of spontaneous behavior tests, including tests of exploration. Our curiosity test consists of placing a number of novel objects in the test arena and allowing the dog to explore the objects. In this test young dogs show significantly more exploration and contact with novel objects than old dogs. In the model dog test, dogs are placed in an arena with a life-size plastic dog. Young dogs again show significantly more investigative sniffing than old dogs. Young dogs spend significantly more time in contact with a human sitting in the middle of the arena than old dogs. These tests can also distinguish cognitively impaired aged dogs from successful agers. Compared to successful agers, age-impaired dogs spend less time interacting with novel objects, less time interacting with humans, and more time reacting to their reflection in a mirror. These results indicate that aging can affect curiosity, exploration and responses to novelty rather than locomotor activity per se.

Descriptors: aging, nervous system, neural coordination, arena, laboratory equipment, behavior test, analytical method, life size plastic dog, equipment, model dog test, analytical method, age associated changes noncognitive behavior changes, investigative sniffing, mirror, meeting abstract.

Siwak, C.T., P.D. Tapp, and N.W. Milgram (2001). **Effect of age and level of cognitive function on spontaneous and exploratory behaviors in the beagle dog**. *Learning and Memory* 8(6) ISSN: 1072-0502.

Abstract: Cognitively characterized young and aged beagle dogs were administered six different spontaneous behavior tests, which provided measures of locomotion, exploration, and social interaction. Consistent with our previous findings, we obtained no overall effect of age on locomotion. We did find, however, that for the aged dogs locomotion correlated with level of cognitive function, being lowest in age-unimpaired dogs and highest in impaired dogs. Exploratory behavior, as measured by response to novelty, varied with age, with young dogs scoring the highest. Young dogs spent more time with novel toys and a person, responded more to a silhouette of a dog, and interacted more with a model dog compared to aged dogs. Among the aged dogs, age-unimpaired dogs spent the greatest amount of time sitting or standing beside a person whereas age-impaired dogs spent the most time reacting to a reflection in a mirror. The age-impaired dogs show undirected, stereotypical types of behavioral patterns. These differences in activity patterns may be linked to underlying age-associated neuropathology.

Descriptors: age differences, animal behavior, Beagle, cognitive development, dog breeds, exploration, locomotion, social interaction, dogs.

Siwak, C.T., P.D. Tapp, and N.W. Milgram (2002). **Behavioural correlates of age-associated cognitive changes in dogs**. *Symposium on brain aging and related behavioral changes in dogs, Orlando, Florida, USA, 11 January 2002,*20-22 p.
Descriptors: abnormal behavior, age, aging, analytical methods, animal behavior, mental ability, dogs.

Siwak, C.T., P.D. Tapp, and N.W. Milgram (2001). **Effect of age and level of cognitive function on spontaneous and exploratory behaviors in the beagle dog**. *Learning and Memory* 8(6): 317-325. ISSN: 1072-0502.
Abstract: Cognitively characterized young and aged beagle dogs were administered six different spontaneous behavior tests, which provided measures of locomotion, exploration, and social interaction. Consistent with our previous findings, we obtained no overall effect of age on locomotion. We did find, however, that for the aged dogs locomotion correlated with level of cognitive function, being lowest in age-unimpaired dogs and highest in impaired dogs. Exploratory behavior, as measured by response to novelty, varied with age, with young dogs scoring the highest. Young dogs spent more time with novel toys and a person, responded more to a silhouette of a dog, and interacted more with a model dog compared to aged dogs. Among the aged dogs, age-unimpaired dogs spent the greatest amount of time sitting or standing beside a person whereas age-impaired dogs spent the most time reacting to a reflection in a mirror. The age-impaired dogs show undirected, stereotypical types of behavioral patterns. These differences in activity patterns may be linked to underlying age-associated neuropathology.
Descriptors: aging, behavior, nervous system, neural coordination, spontaneous behavior test, assessment method, experimental method, age effects, age associated neuropathology, cognitive function, level, exploration, exploratory behavior, locomotion, social interaction, spontaneous behavior.

Skoumalova, A., J. Rofina, Z. Schwippelova, E. Gruys, and J. Wilhelm (2003). **The role of free radicals in canine counterpart of senile dementia of the alzheimer type.** *Experimental Gerontology* 38(6): 711-719. ISSN: 0531-5565.
NAL Call Number: QP86.E85
Abstract: The pathogenesis of Alzheimer's disease is still unknown. In recent time oxidative stress has been discussed as an important contributor. In the present study we investigated the role of free radicals in the spontaneous canine model of Alzheimer's disease. We analysed end-products of lipid peroxidation: lipofuscin-like pigments (LFP), protein carbonyls, and vitamin E to obtain data on oxidative damage in brain of demented dogs. When the generation of free radicals is intensive the toxic products of lipid peroxidation can diffuse from the site of the primary formation and merge with erythrocytes. Therefore we also determined the level of lipid peroxidation in red blood cells. In brain of demented animals the level of LFP increased (to 247%, $P < 0.05$) as well as of protein carbonyls (to 438%, $P < 0.01$) while the vitamin E concentration was lowered (to 34%, $P < 0.01$) when compared to age-matched non-demented controls. The end-products of lipid peroxidation have been found increased also in erythrocytes of demented dogs (250%, $P < 0.05$). These results indicate intensive production of free radicals in brain of animals with dementia which induces damage to erythrocytes. Detection of the specific products of free radical damage in blood samples

could be used for diagnostic purposes.
Descriptors: aging, behavior, metabolism, nervous system, neural coordination, Alzheimer's disease, behavioral and mental disorders, nervous system disease, etiology, senile dementia, lipid peroxidation end products.

Torp, R., E. Head, N.W. Milgram, F. Hahn, O.P. Ottersen, and C.W. Cotman (2000). **Ultrastructural evidence of fibrillar beta-amyloid associated with neuronal membranes in behaviorally characterized aged dog brains**. *Neuroscience* 96(3): 495-506. ISSN: 0306-4522.
Abstract: The aged dog brain accumulates beta-amyloid in the form of diffuse senile plaques, which provides a potentially useful in vivo model system for studying the events surrounding the deposition of beta-amyloid. We used postembedding immunocytochemistry at the electron microscopic level to determine the subcellular distribution of beta-amyloid 1-40 and beta-amyloid 1-42 peptides in the prefrontal and parietal cortex of behaviorally characterized dogs ranging in age from one to 17 years. Immunogold particles signaling beta-amyloid 1-42 occurred over intracellular and extracellular fibrils that were approximately 8 nm in width. Intracellular beta-amyloid 1-42 fibrils were found in close proximity to glial fibrillary acidic protein fibers within astrocytes, but only in cells with signs of plasma membrane disruption. Neuronal labeling of beta-amyloid 1-42 appears to be associated with the plasma membrane. Membrane-bound beta-amyloid 1-42 occurs in the form of fine fibrils that are embedded in the dendritic membrane and appear to project into the extracellular space as determined by quantitative analysis of the immunogold particle distribution. Bundles of beta-amyloid 1-42 were also closely associated and/or integrated with degenerating myelin sheaths of axons. In one dog that was impaired on several cognitive tasks, extensive beta-amyloid 1-42 deposition was associated with microvacuolar changes and vascular pathology. The present findings suggest that beta-amyloid 1-42 may be generated at the dendritic plasma membrane as well as in intracellular compartments. The close association between beta-amyloid 1-42 destroyed myelin suggests one possible new mechanism by which beta-amyloid 1-42 induces neurodegeneration.
Descriptors: nervous system, neural coordination, neurodegeneration, nervous system disease.

Zaucha, J.M., C. Yu, G. Mathioudakis, K. Seidel, G. Georges, G. Sale, M.T. Little, B. Torok Storb, and R. Storb (2001). **Hematopoietic responses to stress conditions in young dogs compared with elderly dogs**. *Blood* 98(2): 322-327. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Clinical observations show that older patients do not tolerate high-dose chemoradiotherapy as well as younger patients. It is unclear whether this is due to age-related differences in their responses to hematopoietic injury or to differential toxicities to other organs. In the present study, 6 young (0.5 years) and 6 elderly (8 years) dogs were challenged with 7 repeated nonlethal doses of 50 or 100 cGy total body irradiation (TBI) each (total 550 cGy), and 21 days of recombinant canine granulocyte-colony stimulating factor (rcG-CSF) after the last TBI dose. Recoveries of absolute neutrophil, platelet, and lymphocyte counts after each TBI dose, responses to rcG-CSF treatment, and telomere lengths in neutrophils were compared before and after the study. No differences were found in recoveries

of neutrophils, platelets, or in responses to rcG-CSF among young and old dogs. In contrast, recoveries were suggestively worse in younger dogs. After rcG-CSF, platelet recoveries were poor in both groups compared with previous platelet recoveries (P<.01). Consequently, 2 old and 3 young dogs were euthanized because of persistent thrombocytopenia and bleeding. At the study's completion, marrow cellularities and peripheral blood counts of the remaining young and elderly dogs were equivalent. The telomere lengths in both groups were significantly reduced after the study versus beforehand (P=.03), but the median attritions of telomeres were not different. It was concluded that aging does not appear to affect hematopoietic cell recoveries after repeated low-dose TBI, suggesting that poor tolerance of radiochemotherapy regimens in older patients may be due to nonhematopoietic organ toxicities rather than age-related changes in hematopoietic stem cells reserves.
Descriptors: aging, pharmacology, radiation biology, blood and lymphatics, transport and circulation, thrombocytopenia, blood and lymphatic disease, radiochemotherapy, radiologic method, therapeutic method, bleeding, hematopoietic responses, stress conditions, total body irradiation.

Zicker, S.C. (2005). **Cognitive and behavioral assessment in dogs and pet food market applications**. *Progress in Neuro Psychopharmacology and Biological Psychiatry* 29(3): 455-459.
Abstract: A multi-disciplinary program was developed to assess the efficacy of antioxidant inclusion in a canine pet food on cognitive decline in aged beagles. A systematic approach to development of the food was used prior to beginning the cognitive studies. Comprehensive evaluation of antioxidant ingredients included assessments of commodities with naturally occurring antioxidants and synthetic antioxidants not commonly utilized, or at different concentrations than what was commonly utilized, in commercial pet foods. Studies were conducted to insure stability through processing, absorption from the gastrointestinal tract, safety, and tests for potential antioxidant biological benefit by ex vivo tests. Testing of the antioxidant-fortified food in aged beagles slowed the rate of cognitive decline in aged dogs. In addition, environmental enrichment also slowed the rate of cognitive decline. Importantly, the combination of dietary antioxidants and environmental enrichment was synergistic and resulted in the least amount of cognitive decline over the 30-month study period. Finally, a clinical study showed that antioxidant fortified food improved age-related behavioral changes in older pet dogs at in-home situations.

Cardiovascular System

Achour, H.C., F. Boccalandro, M.L. Buja, Y.J. Geng, J. Amirian, P. Felli, and R.W. Smalling (2004). **Effects of mechanical left ventricular unloading on endothelin-1 release and apoptosis.** *Journal of the American College of Cardiology* 43(5 Supplement A): 263A-264A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, left anterior descending coronary artery occlusion, lad occlusion, experimental surgical techniques, laboratory techniques, radio immunoassay, immunologic techniques, apoptosis.

Ahlberg, S.E., C.M. Ripplinger, N.D. Skadsberg, P.A. Iaizzo, and L.J. Mulligan (2007). **Effects of pacing rate on mechanical restitution within the in vivo canine heart: study of the force-frequency relationship.** *Journal of Cardiovascular Electrophysiology* 18(2): 212-217.
Abstract: INTRODUCTION: It is known that as stimulation frequency is increased in a healthy heart, a corresponding increase in LV contractile function (dP/dt(max)) is observed, i.e., force-frequency relationship. The impact of this relationship on systolic and diastolic mechanical restitution in an ejecting, in vivo preparation has yet to be explored. Understanding this relationship may lead to further insight on the cellular processes that govern the contraction and relaxation of the heart, in addition to providing a safer, more feasible clinical diagnostic tool. METHODS AND RESULTS: Anesthetized canines (n = 8) were paced from the RA at rates of 130, 150, and 180 bpm. At each rate, extrasystoles were delivered at varying intervals. The LV dP/dt(max) and dP/dt(min) associated with the extrasystolic beat were expressed as a percentage of steady-state levels and plotted as a function of the extrasystolic interval to obtain mechanical restitution curves. The systolic restitution time constant length decreased significantly with all increases in heart rate, $P < 0.05$. In the diastolic case, significant decreases in restitution time constants were seen when heart rate was increased from 130 bpm to 180 bpm, and from 150 bpm to 180 bpm, $P < 0.05$. CONCLUSION: This study was the first to quantify the finding that the time constant of restitution significantly and consistently decreased with a consistent increase in heart rate. The identification of such behavior may be employed to develop stimulation protocols and chronic diagnostic tools to more safely and sensitively identify and optimize the clinical status of patients receiving pacing therapy.
Descriptors: cardiac pacing, artificial methods, myocardial contraction physiology, biomechanics, blood pressure physiology, diastole physiology, dogs, heart rate physiology, linear models, models, animal, recovery of function physiology, systole physiology.

Akar, F.G., R.C. Wu, I. Deschenes, A.A. Armoundas, V.I. Piacentino, S.R. Houser, and G.F. Tomaselli (2004). **Phenotypic differences in transient outward k+ current of human and canine ventricular myocytes: insights into molecular composition of ventricular ito.** *American Journal of Physiology* 286(2 Part 2): H602-H609. ISSN: 0002-9513.

NAL Call Number: 447.8 Am3
Abstract: The Ca2+-independent transient outward K+ current (Ito) plays an important electrophysiological role in normal and diseased hearts. However, its contribution to ventricular repolarization remains controversial because of differences in its phenotypic expression and function across species. The dog, a frequently used model of human cardiac disease, exhibits altered functional expression of Ito. To better understand the relevance of electrical remodeling in dogs to humans, we studied the phenotypic differences in ventricular Ito of both species with electrophysiological, pharmacological, and protein-chemical techniques. Several notable distinctions were elucidated, including slower current decay, more rapid recovery from inactivation, and a depolarizing shift of steady-state inactivation in human vs. canine Ito. Whereas recovery from inactivation of human Ito followed a monoexponential time course, canine Ito recovered with biexponential kinetics. Pharmacological sensitivity to flecainide was markedly greater in human than canine Ito, and exposure to oxidative stress did not alter the inactivation kinetics of Ito in either species. Western blot analysis revealed immunoreactive bands specific for Kv4.3, Kv1.4, and Kv channel-interacting protein (KChIP)2 in dog and human, but with notable differences in band sizes across species. We report for the first time major variations in phenotypic properties of human and canine ventricular Ito despite the presence of the same subunit proteins in both species. These data suggest that differences in electrophysiological and pharmacological properties of Ito between humans and dogs are not caused by differential expression of the K channel subunit genes thought to encode Ito, but rather may arise from differences in molecular structure and/or posttranslational modification of these subunits.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, cardiac disease, western blot analysis, genetic techniques, laboratory techniques, protein chemical techniques, phenotypic differences.

Amado, L., B. Gerber, D.L. Kraitchman, K. Nasir, E. Castillo, B. Rosen, and J.A.C. Lima (2003). **Accurate and objective infarct sizing by contrast enhanced magnetic resonance imaging defined in a canine myocardial infarction model.** *Journal of the American College of Cardiology* 41(6 Supplement A): 469A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular medicine, human medicine, medical sciences, methods and techniques, myocardial infarction, heart disease, vascular disease, contrast enchanced magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, positron emission tomography.

Anzai, T., Y. Iino, T. Kumeno, and R. Yozu (2007). **Feasibility study of a direct endo-aortic clamp balloon.** *ASAIO Journal American Society for Artificial Internal Organs 1992* 53(2): 136-139.
Abstract: We have developed a new end-aortic clamp balloon catheter intended to be inserted directly into, thereby occluding, the ascending aorta. We examined the performance of this catheter in a canine model. We evaluated the extent of migration tolerance of the catheter under cardiopulmonary bypass perfusion in 12 mongrel dogs, weighing 20 kg, under general anesthesia. After institution of cardiopulmonary bypass, this catheter was inserted into the ascending aorta, and the balloon was inflated to occlude the ascending aorta. After

the canine heart was arrested following the administration of cardioplegic solution, balloon migration was examined over a period of 3 hours, with hourly increases in perfusion pressure from 50 mm Hg to 80 mm Hg and finally to 100 mm Hg. After the migration test, ascending aortic wall sections, where the balloon was inflated, were examined microscopically. At internal balloon pressure of 300 to 400 mm Hg, migration occurred at perfusion pressure of > or =90 to 100 mm Hg. No histological differences were observed with use of the balloon catheter, compared with an extra-aortic clamp forceps. Based on these results, this device is safe, feasible, and can adequately occlude the ascending aorta during cardiopulmonary bypass. We conclude that this device is effective in patients weighing 20 kg.
Descriptors: aorta, balloon dilatation instrumentation, monitoring, intraoperative methods, surgical procedures, minimally invasive instrumentation, balloon dilatation adverse effects, catheterization, dogs, feasibility studies, models, animal, monitoring, intraoperative instrumentation, time factors.

Asanuma, H., T. Minamino, S. Sanada, S. Takashima, H. Ogita, A. Ogai, M. Asakura, Y. Liao, Y. Asano, Y. Shintani, J. Kim, Y. Shinozaki, H. Mori, K. Node, S. Kitamura, H. Tomoike, M. Hori, and M. Kitakaze (2004). **Beta-adrenoceptor blocker carvedilol provides cardioprotection via an adenosine-dependent mechanism in ischemic canine hearts**. *Circulation* 109(22): 2773-2779. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Abstract: Background - Carvedilol is a beta-adrenoceptor blocker with a vasodilatory action that is more effective for the treatment of congestive heart failure than other beta-blockers. Recently, carvedilol has been reported to reduce oxidative stress, which may consequently reduce the deactivation of adenosine-producing enzymes and increase cardiac adenosine levels. Therefore, carvedilol may also have a protective effect on ischemia and reperfusion injury, because adenosine mediates cardioprotection in ischemic hearts. Methods and Results - In anesthetized dogs, the left anterior descending coronary artery was occluded for 90 minutes, followed by reperfusion for 6 hours. Carvedilol reduced the infarct size (15.0 +/- 2.8% versus 40.9 +/- 4.2% in controls), and this effect was completely reversed by the nonselective adenosine receptor antagonist 8-sulfophenyltheophylline (45.2 +/- 5.4%) or by an inhibitor of ecto-5'-nucleotidase (44.4 +/- 3.6%). There were no differences of either area at risk or collateral flow among the various groups. When the coronary perfusion pressure was reduced in other dogs so that coronary blood flow was decreased to 50% of the nonischemic level, carvedilol increased coronary blood flow (49.4 +/- 5.6 to 73.5 +/- 7.5 mL cntdot 100 g-1 cntdot min-1; P 0.05) and adenosine release (112.3 +/- 22.2 to 240.6 +/- 57.1 nmol/L; P 0.05) during coronary hypoperfusion. This increase of coronary blood flow was attenuated by either 8-sulfophenyltheophylline or superoxide dismutase. In human umbilical vein endothelial cells cultured with or without xanthine and xanthine oxidase, carvedilol caused an increase of ecto-5'-nucleotidase activity. Conclusions - Carvedilol shows a cardioprotective effect against ischemia and/or reperfusion injury via adenosine-dependent mechanisms.
Descriptors: cardiovascular system, transport and circulation, pharmacology, heart ischemia, heart disease, vascular disease, therapy.

Ashikaga, H., B.A. Coppola, B. Hopenfeld, E.S. Leifer, E.R. McVeigh, and J.H. Omens (2007). **Transmural dispersion of myofiber mechanics: implications for electrical heterogeneity in vivo.** *Journal of the American College of Cardiology* 49(8): 909-16.

NAL Call Number: RC681.A1

Abstract: OBJECTIVES: We investigated whether transmural mechanics could yield insight into the transmural electrical sequence. BACKGROUND: Although the concept of transmural dispersion of repolarization has helped explain a variety of arrhythmias, its presence in vivo is still disputable. METHODS: We studied the time course of transmural myofiber mechanics in the anterior left ventricle of normal canines in vivo (n = 14) using transmural bead markers under biplane cineradiography. In 4 of these animals, plunge electrodes were placed in the myocardial tissue within the bead set to measure transmural electrical sequence. RESULTS: The onset of myofiber shortening was earliest at endocardial layers and progressively delayed toward epicardial layers ($p < 0.001$), resulting in transmural dispersion of myofiber shortening of 39 ms. The onset of myofiber relaxation was earliest at epicardial layers and most delayed at subendocardial layers ($p = 0.004$), resulting in transmural dispersion of myofiber relaxation of 83 ms. There was no significant transmural gradient in electrical repolarization (p = NS). CONCLUSIONS: Despite lack of evidence of significant transmural gradient in electrical repolarization in vivo, there is transmural dispersion of myofiber relaxation as well as shortening.

Descriptors: myocardial contraction physiology, ventricular function, left physiology, biomechanics, blood pressure, dogs, electrocardiography, endocardium physiology, models, animal, pericardium physiology.

Notes: Comment In: J Am Coll Cardiol. 2007 Aug 14;50(7):649-50; author reply 650.

Auchampach, J.A., Z.D. Ge, T.C. Wan, J. Moore, and G.J. Gross (2003). **A3 adenosine receptor agonist ib-meca reduces myocardial ischemia-reperfusion injury in dogs.** *American Journal of Physiology* 285(2 Part 2): H607-H613. ISSN: 0002-9513.

NAL Call Number: 447.8 Am3

Abstract: We examined the effect of the A3 adenosine receptor (AR) agonist IB-MECA on infarct size in an open-chest anesthetized dog model of myocardial ischemia-reperfusion injury. Dogs were subjected to 60 min of left anterior descending (LAD) coronary artery occlusion and 3 h of reperfusion. Infarct size and regional myocardial blood flow were assessed by macrohistochemical staining with triphenyltetrazolium chloride and radioactive microspheres, respectively. Four experimental groups were studied: vehicle control (50% DMSO in normal saline), IB-MECA (100 mug/kg iv bolus) given 10 min before the coronary occlusion, IB-MECA (100 mug/kg iv bolus) given 5 min before initiation of reperfusion, and IB-MECA (100 mug/kg iv bolus) given 10 min before coronary occlusion in dogs pretreated 15 min earlier with the ATP-dependent potassium channel antagonist glibenclamide (0.3 mg/kg iv bolus). Administration of IB-MECA had no effect on any hemodynamic parameter measured including heart rate, first derivative of left ventricular pressure, aortic pressure, LAD coronary blood flow, or coronary collateral blood flow. Nevertheless, pretreatment with IB-MECA before coronary occlusion produced a marked reduction in infarct size (apprx40% reduction) compared with the control group (13.0+-3.2% vs. 25.2+-3.7% of the area at risk, respectively). This effect of IB-MECA was blocked

completely in dogs pretreated with glibenclamide. An equivalent reduction in infarct size was observed when IB-MECA was administered immediately before reperfusion (13.1+-3.9%). These results are the first to demonstrate efficacy of an A3AR agonist in a large animal model of myocardial infarction by mechanisms that are unrelated to changes in hemodynamic parameters and coronary blood flow. These data also demonstrate in an in vivo model that IB-MECA is effective as a cardioprotective agent when administered at the time of reperfusion.

Descriptors: animal model, myocardial ischemia-reperfusion injury, myocardial blood flow, infarct size, coronary occlusion, A3 adenosine receptor, IB-MECA, cardioprotective agent, pharmacology, coronary occlusion, drug therapy, aortic pressure, coronary blood flow, coronary collateral blood flow, heart rate, infarct size, left ventricular pressure.

Auchampach, J.A., X. Jin, J. Moore, T.C. Wan, L.M. Kreckler, Z.D. Ge, J. Narayanan, E. Whalley, W. Kiesman, B. Ticho, G. Smits, and G.J. Gross (2004). **Comparison of three different a1 adenosine receptor antagonists on infarct size and multiple cycle ischemic preconditioning in anesthetized dogs.** *Journal of Pharmacology and Experimental Therapeutics* 308(3): 846-856. ISSN: 0022-3565.

NAL Call Number: 396.8 J82

Abstract: A1 adenosine receptor (AR) antagonists are effective diuretic agents that may be useful for treating fluid retention disorders including congestive heart failure. However, antagonism of A1ARs is potentially a concern when using these agents in patients with ischemic heart disease. To address this concern, the present study was designed to compare the actions of the A1AR antagonists CPX (1,3-dipropyl-8-cyclopentylxanthine), BG 9719 (1,3-dipropyl-8-(2-(5,6-epoxynorbomyl))xanthine), and BG 9928 (1,3-dipropyl-8-(1-(4-propionate)-bicyclo-(2,2,2)octyl)xanthine) on acute myocardial ischemia/reperfusion injury and ischemic preconditioning (IPC) in an in vivo dog model of infarction. Barbital-anesthetized dogs were subjected to 60 min of left anterior descending coronary artery occlusion followed by 3 h of reperfusion, after which infarct size was assessed by staining with triphenyltetrazolium chloride. IPC was elicited by four 5-min occlusion/5-min reperfusion cycles produced 10 min before the 60-min occlusion. Multiple-cycle IPC produced a robust reduction (apprx65%) in infarct size; this effect of IPC on infarct size was not abrogated in dogs pretreated with any of the three AR antagonists. Surprisingly, in the absence of IPC, pretreatment with CPX or BG 9928 before occlusion or immediately before reperfusion resulted in significant reductions (apprx40-50%) in myocardial infarct size. However, treatment with an equivalent dose of BG 9719 had no similar effect. We conclude that the A1AR antagonists BG 9719, BG 9928, and CPX do not exacerbate cardiac injury and do not interfere with IPC induced by multiple ischemia/reperfusion cycles. We discuss the possibility that the cardioprotective actions of CPX and BG 9928 may be related to antagonism of A2BARs.

Descriptors: cardiovascular system, transport and circulation, pharmacology, acute myocardial ischemia, reperfusion injury, heart disease, injury, vascular disease, ischemic preconditioning.

Baba, S., W. Dun, and P.A. Boyden (2003). **Can pka activators restore na+ channel function in cells from the canine infarcted heart?** *Biophysical Journal* 84(2 Part 2): 549A. ISSN: 0006-3495.

NAL Call Number: 442.8 B5238
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, membranes, cell biology, myocardial infarction, heart disease, vascular disease, patch clamp, histology and cytology techniques, laboratory techniques.

Bal, H., E.V. Dibella, and G.T. Gullberg (2003). **Myocardial assessment with dynamic teboroxime spect in a reperfused canine model.** *Journal of Nuclear Medicine* 44 (5 Supplement): 113P. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, cardiac single photon emission computed tomography imaging, imaging and microscopy techniques, laboratory techniques, myocardial assessment, myocardial blood flow, myocardial viability.

Banerjee, D.D., M.S. Quinn, L.B. Mohanty, and A.J. Minisi (2008). **Failure of chronic transmyocardial laser revascularization to alter cardiac nociceptive reflexes: implications for the treatment of angina pectoris.** *Lasers in Medical Science* 23(2): 155-61. ISSN: 0268-8921.
Abstract: The aim of this study was to assess the delayed effects of transmyocardial laser revascularization (TMLR) on cardiac nociceptors. Experiments were performed in anesthetized dogs 1 month after thoracotomy with either TMLR (n = 17) or sham laser procedure (n = 17). All dogs underwent sinoaortic denervation and vagotomy to isolate the sympathetic afferent system. Left ventricular sympathetic afferents were stimulated by intracoronary bradykinin and transmural myocardial ischemia. Efferent responses were measured by direct recording of renal sympathetic nerve activity. Renal nerve responses to intracoronary bradykinin administered to the laser-treated anterior ventricular wall were not significantly different from those observed from the unlased posterior wall. Anterior transmural ischemia elicited similar renal nerve responses in laser-treated and sham groups. Pathologic analysis showed intact neural structures in the subepicardial regions both near and remote from the lased channels. We conclude that reflexes mediated by left ventricular sympathetic afferents are preserved after chronic TMLR. These findings do not support the neural hypothesis for angina relief.
Descriptors: angina pectoris therapy, heart innervation, heart ventricles innervation, laser therapy methods, nociceptors radiation effects, treatment failure, chronic disease, dogs, heart physiology, laser therapy instrumentation, models, animal, myocardial ischemia therapy, myocardium, sympathetic nervous system, thoracotomy, time factors, ventricular function.

Banyasz, T., L. Fulop, J. Magyar, N. Szentandrassy, A. Varro, and P.P. Nanasi (2003). **Endocardial versus epicardial differences in l-type calcium current in canine ventricular myocytes studied by action potential voltage clamp.** *Cardiovascular Research* 58(1): 66-75. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: Objectives: The aim of the present study was to assess and compare the dynamics of L-type Ca2+ current (ICa,L) during physiologic action potential (AP) in canine ventricular cardiomyocytes of epicardial (EPI) and endocardial (ENDO) origin. Methods: ICa,L was recorded on cells derived from the two regions of the heart using both AP voltage clamp and

conventional whole cell voltage clamp techniques. Results: AP voltage clamp experiments revealed that the decay of ICa,L is monotonic during endocardial AP, whereas the current is double-peaked (displaying a second rise) during epicardial AP. The amplitude of the first peak was significantly greater in ENDO (-4.6+-0.8 pA/pF) than in EPI cells (-2.8+-0.3 pA/pF). Application of epicardial APs as command pulses to endocardial cells yielded double-peaked ICa,L profiles, and increased the net charge entry carried by ICa,L during the AP from 0.187+-0.059 to 0.262+-0.056 pC/pF (n=5, P<0.05). No differences were observed in current densities and inactivation kinetics of ICa,L between EPI and ENDO cells when studied under conventional voltage clamp conditions. Nisoldipine shortened action potentials and eliminated the dome of the epicardial AP. Conclusion: ICa,L was shown to partially inactivate before and deactivate during phase-1 repolarization and reopening of these channels is responsible for the formation of the dome in canine EPI cells. The transmural differences in the profile of ICa,L could be well explained with differences in AP configuration. **Descriptors:** biochemistry and molecular biophysics, cardiovascular system, transport and circulation, cell biology, methods and techniques, action potential.

Bashar, A.H., K. Suzuki, T. Kazui, M.Y. Okada, T. Suzuki, N. Washiyama, H. Terada, and K. Yamashita (2008). **Changes in cerebrospinal fluid and blood lactate concentrations after stent-graft implantation at critical aortic segment: a preliminary study.** *Interactive Cardiovascular and Thoracic Surgery* 7(2): 262-6.

Abstract: OBJECTIVES: Obstruction of blood flow through the arteria radicularis magna (ARM) has been linked with ischemic spinal cord injury after conventional thoracic aortic repair. Whether or not endoluminal stent-grafts, deliberately positioned against this artery can cause similar damage to the spinal cord has not been comprehensively investigated. The purpose of this study was to assess the blood and cerebrospinal fluid (CSF) concentrations of lactate - a well-known biochemical marker of ischemic neurological injury, before and after stent-graft implantation against the ARM. MATERIALS AND METHODS: Endoluminal stent-grafting was performed in ten mongrel dogs. In five animals (experimental group), stent-grafts covered the fourth and fifth lumbar segmental arteries - which have been described as the canine equivalents to the ARM in humans. In the remaining five animals (control group), devices of similar length were placed in the lower thoracic aorta. CSF was obtained by cisternal puncture technique at the following time points; before stent-grafting, and 15, 30 and 60 min after stent-grafting. Parallel arterial blood samples were also obtained using a heparinized syringe. All samples were centrifuged and the supernatant analysed for lactate. RESULTS: The mean preprocedural lactate concentration in the CSF was 1.7+/-0.3 mmol/l. Mean postprocedural levels in the experimental group at 15, 30 and 60 min were 3.1+/-1.9, 3.9+/-1.1 and 11.9+/-2.5 mmol/l, respectively (control values; 2.1+/-1.9, 2.7+/-1.1 and 1.9+/-1.5 mmol/l, respectively). Mean preprocedural blood lactate level was 1.8+/-0.6 mmol/l, while the mean postprocedural concentrations in the experimental group at 15, 30 and 60 min were 2.9+/-1.2, 3.4+/-1.7 and 3.9+/-2.0 mmol/l, respectively. Two out of the five animals in the experimental group suffered mild to moderate hind limb weakness. CONCLUSION: Selective placement of stent-grafts against the ARM in dogs resulted in a conspicuous increase in CSF and blood lactate concentrations 60 min after the procedure with or without physical signs of neurological deficits. Although the small sample size of this preliminary study does not allow any definitive conclusion, it may be worthwhile to confirm

the findings in appropriately controlled larger studies.
Descriptors: blood vessel prosthesis, blood vessel prosthesis implantation adverse effects, lactic acid metabolism, spinal cord ischemia etiology, stents, thoracic arteries surgery, aortography, biological markers metabolism, blood vessel prosthesis implantation instrumentation, dogs, lactic acid blood, lactic acid cerebrospinal fluid, models, animal, motor activity, pilot projects, prosthesis design, spinal cord ischemia metabolism, spinal cord ischemia physiopathology, thoracic arteries radiography, time factors, up regulation.

Basso, C., P.R. Fox, K.M. Meurs, J.A. Towbin, A.W. Spier, F. Calabrese, B.J. Maron, and G. Thiene (2004). **Arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death in boxer dogs: a new animal model of human disease.** *Circulation* 109(9): 1180-1185. ISSN: 1524-4539.
NAL Call Number: RC681.A1 C8
Abstract: BACKGROUND: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary familial heart muscle disease associated with substantial cardiovascular morbidity and risk of sudden death. Efforts to discern relevant pathophysiological mechanisms have been impaired by lack of a suitable animal model. METHODS AND RESULTS: ARVC was diagnosed in 23 boxer dogs (12 male; 9.1+/-2.3 years old). Clinical events alone or in combination included sudden death (n=9; 39%), ventricular arrhythmias of suspected right ventricular (RV) origin (n=19; 83%), syncope (n=12, 52%), and heart failure (n=3; 13%). Right ventricular enlargement or aneurysms occurred in 10 (43%). Striking histopathological abnormalities were present in each boxer dog but not in controls, including severe RV myocyte loss with replacement by fatty (n=15, 65%) or fibrofatty (n=8, 35%) tissue. Focal fibrofatty lesions were also present in both atria (n=8) and the left ventricle (LV) (n=11). Fatty replacement occupied substantially greater RV wall area in ARVC dogs than controls (40.4+/-18.8% versus 13.8+/-3.4%, respectively) (P<0.001); residual myocardium was correspondingly reduced (56.6+/-19.2% versus 84.8+/-3.8% in controls) (P<0.001). MRI demonstrated bright anterolateral and/or infundibular RV myocardial signals, confirmed as fat by histopathology. Myocarditis appeared in the RV (n=14, 61%) and LV (n=16, 70%) and in each dog with sudden death, but not in controls. Familial transmission was evident in 10 of the 23. CONCLUSIONS: We describe a novel, spontaneous, and genetically transmitted animal model of ARVC associated with sudden death in the boxer dog, closely resembling the human disease. This model may aid in understanding the pathogenic mechanisms of ARVC.
Descriptors: boxer dog, genetically transmitted animal model, arrhythmogenic right ventricular cardiomyopathy (ARVC), morbidity risk, histopathological abnormalities.

Bauer, A., J.K. Donahue, F. Voss, R. Becker, P. Kraft, J.C. Senges, K. Kelemen, H.A. Katus, and W. Schoels (2004). **Pro- and antiarrhythmic effects of fast cardiac pacing in a canine model of acquired long qt syndrome**. *Naunyn Schmiedeberg's Archives of Pharmacology* 369(4): 447-454. ISSN: 0028-1298.
NAL Call Number: 448.8 AR2
Abstract: Increasing the heart rate is one option for suppressing bradycardia-dependent polymorphic ventricular tachycardias (PVTs). The mechanisms underlying preventive pacing in acquired forms of the long QT syndrome (LQTs) are still not fully understood. Using

two needle electrodes, local effective refractory periods (ERPs) were determined in the left (LV) and right ventricle (RV) in 20 dogs with acute AV node ablation before continuous pacing, during a 20-min period of continuous fast pacing (Cl 300 ms, fastpac) and during a 35-min recovery period with slow (Cl 500 ms) pacing. This protocol was applied to control dogs (5 dogs) and dogs with pretreatment of the IKs blocking agent chromanol 293b (5 dogs, LQTs1), the IKr-blocking agent dofetilide (5 dogs, LQTs2) or a combination thereof (5 dogs). Fastpac resulted in a significant abbreviation of ERPs in control dogs and dogs receiving dofetilide or chromanol 293b. During recovery, shortening of ERPs persisted in the control group, but diminished in dogs with acquired LQTs. In dogs with LQTs2 fastpac could not suppress inhomogeneity of refractoriness during recovery. With pretreatment of dofetilide and chromanol 293b in combination, MAP duration during fastpac significantly increased (first beat: 256+/-6 ms vs. sixth beat: 278+/-9 ms, $p<0.05$) and fastpac-induced PVTs were evident. ERP shortening and reduced inhomogeneity of refractoriness might be one antiarrhythmic action of fastpac in dogs with acute AV-block. However, in the acquired LQTs1 and 2 beneficial effects of fastpac diminished and in a combination thereof fastpac-induced PVTs are likely.

Descriptors: cardiovascular system, transport and circulation, acquired long QT syndrome, heart disease, polymorphic ventricular tachycardia, heart disease, fast cardiac pacing, antiarrhythmic effects, proarrhythmic effects, heart rate.

Bayar, M.A., Y. Erdem, K. Ozturk, O. Bescalti, M. Caydere, D. Yucel, Z. Buharali, and H. Ustun (2003). **The effect of egb-761 on morphologic vasospasm in canine basilar artery after subarachnoid hemorrhage.** *Journal of Cardiovascular Pharmacology* 42(3): 395-402. ISSN: 0160-2446.

Abstract: This study investigated the effects of Ginkgo biloba extract (EGb-761), an anti-oxidant and platelet-activating factor antagonist, on basilar artery vasospasm in an experimental canine subarachnoid hemorrhage model. Morphometric analyses were performed, and serum and cerebrospinal fluid endothelin-1 levels were measured by radioimmunoassay. Comparisons were made between treated and untreated groups. Twenty-four mongrel dogs were randomly assigned to three groups. The animals in group 1 (n=8) were not subjected to subarachnoid hemorrhage and received no treatment. In this group, serum and cerebrospinal fluid endothelin-1 levels were measured daily for 8 days. On day 9, the animals were killed and their basilar arteries were excised for histopathological examination. In group 2 (n=8), subarachnoid hemorrhage was produced using autologous arterial blood, and daily intravenous boluses of saline were administered for the next 8 days. Assessments of endothelin-1 levels and the basilar arteries were performed as described for group 1. In group 3 (n=8), subarachnoid hemorrhage was produced using autologous arterial blood, and daily intravenous boluses of EGb-761 were administered for 8 days. Endothelin-1 levels and the basilar arteries were assessed as described above. The groups' serum endothelin-1, cerebrospinal fluid endothelin-1, and histopathological findings were compared. In group 1, the serum and cerebrospinal fluid endothelin-1 levels did not change significantly over the 8 days, and histopathological examination of the basilar arteries revealed no abnormalities. In group 2, the serum and cerebrospinal fluid endothelin-1 levels increased abruptly and significantly on day 2, and remained high to the end of the study period (day 8). Histopathological examination revealed marked vasospasm. In group 3, the serum and cerebrospinal fluid endothelin-1 levels

followed the same pattern observed in group 2; however, the arteries showed significantly less vasospasm than that observed in group 2. The study findings did not provide information about the mechanism of action of the platelet-activating factor-antagonist EGb-761, but they clearly show that this agent decreases morphologic vasospasm in the dog basilar artery.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacognosy, pharmacology, cerebral vasospasm, nervous system disease, vascular disease, subarachnoid hemorrhage.

Behringer, W., P. Safar, X. Wu, R. Kentner, A. Radovsky, P.M. Kochanek, C.E. Dixon, and S.A. Tisherman (2003). **Survival without brain damage after clinical death of 60-120 mins in dogs using suspended animation by profound hypothermia.** *Critical Care Medicine* 31(5): 1523-31. ISSN: 0090-3493.
Abstract: OBJECTIVES: This study explored the limits of good outcome of brain and organism achievable after cardiac arrest (no blood flow) of 60-120 mins, with preservation (suspended animation) induced immediately after the start of exsanguination cardiac arrest. DESIGN: Prospective experimental comparison of three arrest times, without randomization. SETTING: University research laboratory. SUBJECTS: Twenty-seven custom-bred hunting dogs (17-25 kg). INTERVENTIONS: Dogs were exsanguinated over 5 mins to cardiac arrest no-flow of 60 mins, 90 mins, or 120 mins. At 2 mins of cardiac arrest, the dogs received, via a balloon-tipped catheter, an aortic flush of isotonic saline at 2 degrees C (at a rate of 1 L/min), until tympanic temperature reached 20 degrees C (for 60 mins of cardiac arrest), 15 degrees C (for 60 mins of cardiac arrest), or 10 degrees C (for 60, 90, or 120 mins of cardiac arrest). Resuscitation was by closed-chest cardiopulmonary bypass, postcardiac arrest mild hypothermia (tympanic temperature 34 degrees C) to 12 hrs, controlled ventilation to 20 hrs, and intensive care to 72 hrs. MEASUREMENTS AND MAIN RESULTS: We assessed overall performance categories (OPC 1, normal; 2, moderate disability; 3, severe disability; 4, coma; 5, death), neurologic deficit scores (NDS 0-10%, normal; 100%, brain death), regional and total brain histologic damage scores at 72 hrs (total HDS >0-40, mild; 40-100, moderate; >100, severe damage), and morphologic damage of extracerebral organs. For 60 mins of cardiac arrest (n = 14), tympanic temperature 20 degrees C (n = 6) was achieved after flush of 3 mins and resulted in two dogs with OPC 1 and four dogs with OPC 2: median NDS, 13% (range 0-27%); and median total HDS, 28 (range, 4-36). Tympanic temperature of 15 degrees C (n = 5) was achieved after flush of 7 mins and resulted in all five dogs with OPC 1, NDS 0% (0-3%), and HDS 8 (0-48). Tympanic temperature 10 degrees C (n = 3) was achieved after flush of 11 mins and resulted in all three dogs with OPC 1, NDS 0%, and HDS 16 (2-18). For 90 mins of cardiac arrest (n = 6), tympanic temperature 10 degrees C was achieved after flush of 15 mins and resulted in all six dogs with OPC 1, NDS 0%, and HDS 8 (0-37). For 120 mins of cardiac arrest (n = 7), three dogs had to be excluded. In the four dogs within protocol, tympanic temperature 10 degrees C was achieved after flush of 15 mins. This resulted in one dog with OPC 1, NDS 0%, and total HDS 14; one with OPC 1, NDS 6%, and total HDS 20; one with OPC 2, NDS 13%, and total HDS 10; and one with OPC 3, NDS 39%, and total HDS 22. CONCLUSIONS: In a systematic series of studies in dogs, the rapid induction of profound cerebral hypothermia (tympanic temperature 10 degrees C) by aortic flush of cold saline immediately after the start of exsanguination cardiac arrest-which rarely can be resuscitated effectively with current methods-can

achieve survival without functional or histologic brain damage, after cardiac arrest no-flow of 60 or 90 mins and possibly 120 mins. The use of additional preservation strategies should be pursued in the 120-min arrest model.
Descriptors: animal model, cardiac arrest, brain damage, organ damage, resuscitation.

Bhattacharyya, M.L., K.P. Mull, Q. Debnam, S. Kabir, and A. Ivy (2003). **Contrasting roles of a novel k+ channel blocker and a k+ channel opener on electro-mechanical activity in canine heart tissue.** *International Journal of Cardiology* 89(1): 71-78. ISSN: 0167-5273.
Abstract: We tested the effects of a potassium channel opener diazoxide on the action potential duration (APD) and contractile force changes in canine Purkinje tissue induced by a novel class III anti-arrhythmic agent (C3A), KCB-328 (0.5 muM) with 3,4-dimethoxy-phenethyl ring structure (0.5 muM). KCB-328 shortened APD25 by 8.3+-2.1%, prolonged APD50 and APD90 by 31.2+-5.3 and 50.0+-7.1%, respectively. Diazoxide (0.1 mM) shortened APD at all levels by 58.3+-8.1, 54.1+-6.1, and 42.8+-5.8%, respectively. In the presence of diazoxide, KCB-328 still prolonged APD50 and APD90 (12.5+-3.8 and 26.8+-5.9%, respectively). KCB-328 increased force of contraction in a dose-dependent manner. KCB-328 increased force less in the presence of diazoxide. Administration of diazoxide only, reduced force of contraction. We conclude that APD prolongation by KCB-328 may occur even in the presence of diazoxide. It is not sufficient for the restoration of already diminished contractile force and that such an APD prolongation may be unrelated to the restoration of force of contraction even though both are most often seen to occur simultaneously.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, action potential duration, prolongation.

Bin Jianping , K. Wei, and R.A. Pelberg (2000). **Dipyridamole stress myocardial contrast echocardiography in detection coronary stenosis: a chest closed dog trial**. *Zhongguo Chaosheng Yixue Zazhi* 16(6): 409-412. ISSN: 1002-0101.
Abstract: Objective: To assess the accuracy of myocardial contrast echocardiography (MCE) in combination with dipyridamole stress in detecting non-flow-limited coronary stenoses at rest. Methods: MCE was performed by intravenous injection of microbubbles (MRX-115) and radiolabled microspheres to measure myocardial blood flow (MBF)in 17 chest closed dogs. Chronical instrumental coronary stenoses models were created by placing ameroid contrictors. Data were acquired in 7-10 post-operative days. Results: No perfusion defects were noted at baseline. However, perfusion defects were seen in abnormal beds (MBF reserve<3) during dipyridamole stress. The peak video intensity(VI)in the abnormal beds was lower (33+-13 ver 50+-12; P<0. 01)than in normal beds with dipyridamole. An excellent linear relation was noted between the peak VI ratio (0. 6+-0. 2, abnormal/normal) and that of MBF using dipyridamole (r = 0. 89, P< 0. 0001). Conclusion: MCF with dipyridamole may be clinically useful for the detection and quantification of coronary stenoses.
Descriptors: radiology, medical sciences, cardiovascular system, transport and circulation, coronary stenosis, vascular disease, diagnosis, non flow limited, ameroid constrictor placement, surgical method, dipyridamole stress myocardial contrast echocardiography, accuracy, diagnostic method, myocardial blood flow.
Language of Text: Chinese.

Boswood, A. and A. Murphy (2006). **The effect of heart disease, heart failure and diuresis on selected laboratory and electrocardiographic parameters in dogs.** *Journal of Veterinary Cardiology* 8(1): 1-9. ISSN: 1760-2734.
NAL Call Number: SF811
Abstract: Objectives: To evaluate the influence of heart disease and heart failure on 9 parameters: the serum sodium, potassium, chloride, creatinine and urea concentrations, heart rate, vaso-vagal tonus index (VVTI), red cell number and hematocrit. Background: Previous studies have demonstrated that heart disease, heart failure and their treatment are associated with changes in laboratory and electrocardiographic parameters. Animals, materials and methods: Data were retrieved from 92 client-owned dogs with naturally occurring heart disease. Dogs were classified according to the severity of their heart disease and or the presence of heart failure. The effects of heart disease, the progression into heart failure, the initiation of successful therapy and the administration of diuretics on these parameters were determined. Results: Worse heart failure was characterized by the following changes: a significant fall in serum sodium and chloride concentrations and VVTI, and a significant increase in the serum urea concentration and heart rate. The onset of heart failure was characterized by a fall in VVTI and chloride concentration. The successful treatment of heart failure was characterized by a fall in heart rate, an increase in creatinine and sodium concentrations. Dogs receiving diuretics had higher heart rates, lower VVTI, higher urea concentrations, lower potassium, sodium and chloride concentrations. Conclusions: Numerous complex alterations in some of the studied parameters are associated with heart disease, heart failure and their treatment. Further consideration of these changes may improve our skills in diagnosis, prognostication and treatment..
Descriptors: blood composition, creatinine, diagnosis, diuresis, electrocardiography , haematocrit, heart, heart diseases, heart rate, medical treatment, potassium, potassium chloride, sodium, urea.

Briot, R., S. Bayat, D. Anglade, J.L. Martiel, and F.A. Grimbert (2003). **Increased cardiac output induced by terbutaline may recruit injured capillaries during recovery from oleic acid lung injury.** *FASEB Journal* 17(4-5): Abstract No. 562.10. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: terbutaline, a beta 2-agonist, cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, lung injury, injury, respiratory system disease, chemically induced, broncho alveolar lavage technique, laboratory techniques, capillary alveolar macromolecular permeability [camp], cardiac input, microvascular permeability.

Burashnikov, A. and C. Antzelevitch (2008). **Can inhibition of IKur promote atrial fibrillation?** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 5(9): 1304-9.
Abstract: BACKGROUND: Block of ultrarapid delayed rectified potassium current (I(Kur)), present in atria but not in ventricles, is thought to be a promising approach for atrial-specific therapy of atrial fibrillation (AF). However, it has been shown that I(Kur) block may abbreviate atrial repolarization and that loss-of-function mutations in KCNA5, which encodes K(v) 1.5 channels responsible for I(Kur), is associated with familial AF. OBJECTIVE: Our objective in this study was to use low concentrations of 4-aminopyridine (4-AP, 10 to 50 microM), known to selectively block I(Kur), to assess the proarrhythmic and antiarrhyth-

mic effects of I(Kur) block in healthy and remodeled atria. METHODS: Isolated canine coronary-perfused right atrial preparations were used. Acetylcholine or ischemia/reperfusion was used to acutely remodel the atria. Transmembrane action potentials and a pseudo-electrocardiogram were simultaneously recorded. RESULTS: Normal (healthy) atria typically displayed action potentials (AP) with a prominent plateau, whereas remodeled atria displayed triangular-shaped APs (remodeled). In healthy atria, in which AF could not be induced with programmed stimulation, 4-AP abbreviated action potential measured at 90% repolarization (APD(90)) and effective refractory period (ERP), permitting the induction of AF in 4 of 12 preparations (33%). In remodeled atria, 4-AP produced little (50 microM) to no (10 to 25 microM) prolongation of APD(90) or ERP and was either ineffective or poorly effective in terminating AF or preventing its induction. CONCLUSION: Our findings suggest that block of I(Kur) can provide the substrate for development of AF in healthy canine atria, presumably via abbreviation of APD and ERP.
Descriptors: 4 aminopyridine pharmacology, atrial fibrillation drug therapy, heart atria innervation, potassium channel blockers pharmacology, potassium channels drug effects, action potentials drug effects, anti arrhythmia agents therapeutic use, atrial fibrillation physiopathology, delayed rectifier potassium channels drug effects, dogs, heart atria drug effects, heart atria physiopathology, models, animal, potassium channels, voltage gated drug effects, risk factors.

Cardinal, R., C. Bouchard, M. Vermeulen, and P. Page (2000). **Creation of a monomorphic ventricular tachycardia substrate in a canine chronic preparation of stable myocardial hypoperfusion and tachycardia-induced energetic stress**. *Canadian Journal of Cardiology* 16 (Supplement F): 186F. ISSN: 0828-282X.
Descriptors: biochemistry and molecular biophysics, membranes, cell biology, cardiovascular system, transport and circulation, energetic stress, monomorphic ventricular tachycardia, myocardial hypoperfusion, sodium ion current, meeting abstract.

Cesselli, D., I. Jakoniuk, L. Barlucchi, A.P. Beltrami, T.H. Hintze, B. Nadal Ginard, J. Kajstura, A. Leri, and P. Anversa (2001). **Oxidative stress-mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy**. *Circulation Research* 89(3): 279-286. ISSN: 0009-7330.
NAL Call Number: RC681.A1A57137
Abstract: Cell death has been questioned as a mechanism of ventricular failure. In this report, we tested the hypothesis that apoptotic death of myocytes, endothelial cells, and fibroblasts is implicated in the development of the dilated myopathy induced by ventricular pacing. Accumulation of reactive oxygen products such as nitrotyrosine, potentiation of the oxidative stress response by p66shc expression, formation of p53 fragments, release of cytochrome c, and caspase activation were examined to establish whether these events were coupled with apoptotic cell death in the paced dog heart. Myocyte, endothelial cell, and fibroblast apoptosis was detected before indices of severe impairment of cardiac function became apparent. Cell death increased with the duration of pacing, and myocyte death exceeded endothelial cell and fibroblast death throughout. Nitrotyrosine formation and p66shc levels progressively increased with pacing and were associated with cell apoptosis. Similarly, p50 (DELTAN) fragments augmented paralleling the degree of cell death in the

failing heart. Moreover, cytochrome c release and activation of caspase-9 and -3 increased from 1 to 4 weeks of pacing. In conclusion, cardiac cell death precedes ventricular decompensation and correlates with the time-dependent deterioration of function in this model. Oxidative stress may be critical for activation of apoptosis in the overloaded heart.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, dilated cardiomyopathy, heart disease, heart failure, ventricular dysfunction, apoptosis, cell death, oxidative stress.

Cha, S.H., M.H. Han, Y.H. Choi, C.J. Yoon, S.K. Baik, S.J. Kim, and K.H. Chang (2003). **Vascular responses in normal canine carotid arteries: comparison between various self-expanding stents of the same unconstrained size.** *Investigative Radiology* 38(2): 95-101. ISSN: 0020-9996.
Abstract: RATIONALE AND OBJECTIVES: To compare long-term vascular responses upon the insertion of various self-expandable stents, all the same unconstrained size, in canine carotid artery models. MATERIALS AND METHODS: Twenty-two stents (5 SMARTs, 5 Wallstents, 6 Niti-Ss, 6 Niti-Ds) of the same unconstrained size (6 mm in diameter, 20 mm in length) were endovascularly placed in canine common carotid arteries. The luminal changes were measured on three occasions, on prestenting, immediate poststenting, and angiograms taken before specimens were killed. After en-bloc harvest of the stented carotid arteries at 6 months, the intraluminal surface was evaluated by gross observation and scanning electron microscopy (SEM). Neointimal thickness was measured at several points both over the wire and between the wires. RESULTS: Niti-D was excluded from analysis because of high rate of poststenting occlusion. SMART stent showed the greatest expansibility with average initial luminal gain ($P<0.05$) of 21.2% (Niti-S: 16.5%, Wallstent: 12.9%). At 6 months follow-up, the dilated arterial lumen had returned almost to the prestenting caliber without any significant differences among the stent types ($P>0.05$). The thickness of neointimal coverage was more prominent with SMART stent (354 mum over the wire and 258 mum between the wires) than Niti-S (228 mum and 83 mum) or Wallstent (187 mum and 78 mum). CONCLUSION: Stent types with its higher initial luminal gain appeared to be associated with thicker neointimal formation at 6 months. The acute expanding force of a self-expanding stent may be the key to the cause of neointimal hyperplasia. Regardless of the inserted stent type, the variations in neointimal response were offset by luminal gains of varying degree, thus preserving the arterial patency almost to the prestenting size.
Descriptors: cardiovascular system, transport and circulation, equipment apparatus devices and instrumentation, neointimal hyperplasia, vascular disease, smart self expandable stent, medical equipment, wall stent, medical equipment, angiogram, clinical techniques, diagnostic techniques, scanning electron microscopy, imaging and microscopy techniques, laboratory techniques, stent size, stent type.

Chin, B.B., G. Esposito, and D.L. Kraitchman (2002). **Myocardial contractile reserve and perfusion defect severity with rest and stress dobutamine 99mtc-sestamibi spect in canine stunning and subendocardial infarction**. *Journal of Nuclear Medicine* 43(4): 540-550. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Abstract: Myocardial contractile reserve and resting perfusion scintigraphy provide inde-

pendent information to assess myocardial viability. The purpose of this study was to simultaneously evaluate both with 99mTc-sestamibi SPECT and low-dose dobutamine in canine stunning and subendocardial infarction (SEMI). Methods: Eighteen dogs were included in the study: 7 normal, 7 stunned, and 4 with SEMI. Closed-chest stunning and SEMI were produced by angioplasty balloon occlusion of the left anterior descending artery (20 and 90 min, respectively). Subsequent radiolabeled mircospheres confirmed reflow, and 99mTc-sestamibi was then administered at rest. Gated SPECT and MRI tagging were performed at rest and during low-dose dobutamine infusion (5 mug/kg/min). SPECT systolic wall thickening index (SWI) and MRI radial strain quantified myocardial contraction. Postmortem 2,3,5-triphenyltetrazolium chloride staining quantified SEMI. Results: Defect severity by SPECT in the anterior wall was mild and was not statistically different for the stunned versus SEMI groups (P=not significant). At rest, anterior wall SPECT SWI was significantly higher in the normal versus stunned groups (21.1+-3.1 vs. 10.1+-9.0; P=0.0002) and the normal versus SEMI groups (21.1+-3.1 vs. 2.6+-6.0; P=0.000002). With low-dose dobutamine, SWI increased significantly compared with rest for the stunned group (29.1+-10.4 vs. 10.1+-9.0; P=0.000007) but did not increase significantly for the SEMI group (11.0+-11.3 vs. 2.6+-6.0; P=0.09); SWI during low-dose dobutamine infusion for the stunned group was comparable to that for the normal group (29.1+-10.4 vs. 28.2+-7.0; P=0.80). SWI also showed correlation with MRI radial strain (r=0.42; P=0.00015). Conclusion: Defect severity for stunned myocardium and SEMI was mild and was not significantly different. Contractile reserve was significantly different in stunned myocardium and SEMI. 99mTc-Sestamibi SPECT at rest and with low-dose dobutamine is a promising new technique to simultaneously assess myocardial perfusion and contractile reserve.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, radiation biology, myocardial infarction, heart disease, vascular disease, myocardial stunning, subendocardial infarction, heart disease, magnetic resonance imaging, imaging techniques, imaging method, technetium 99m sestamibi spect, technetium 99m sestamibi single photon emission computed tomography, imaging method, rest, stress.

Cho, S., S. Zhang, H. Ureshino, T. Hara, S. Tomiyasu, and K. Sumikawa (2003). **Hemodynamic interactions of propofol and dantrolene in chronically instrumented dogs.** *Anesthesia and Analgesia* 96(5): 1369-1373. ISSN: 0003-2999.
Abstract: The hemodynamic interaction of dantrolene, a specific drug for malignant hyperthermia, and propofol which appears to be safe in malignant hyperthermia-susceptible patients, has not been investigated. We performed this study to examine the hemodynamic actions of dantrolene at a therapeutic dose during propofol anesthesia. Ten dogs were chronically instrumented for the measurements of systemic and coronary hemodynamics. The dogs were assigned to receive propofol with vehicle or dantrolene in a random manner on separate experimental days. Propofol significantly decreased mean arterial blood pressure, left ventricular systolic and end-diastolic pressure, the maximal rate of increase in left ventricular pressure, and left ventricular regional segment shortening. Coronary blood flow (CBF) was unchanged but coronary vascular resistance (CVR) decreased. Dantrolene reversed the decrease in mean arterial blood pressure and left ventricular systolic pressure caused by propofol, and significantly increased heart rate. However, left ventricular end-diastolic pressure, cardiac output, maximal rate of increase in left ventricular pressure, and segment

shortening were unchanged. CBF was significantly increased with a decrease in CVR. These results suggest that dantrolene reverses the hypotensive action produced by propofol and causes an increase in CBF with a decrease in CVR, but does not significantly change the negative inotropic effects. Thus, dantrolene exerts favorable hemodynamic effects during propofol anesthesia.

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, malignant hyperthermia, metabolic disease, muscle disease, drug induced, cardiac output, coronary blood flow, drug drug interaction, mean arterial blood pressure.

Chou, C.C., B.L. Nguyen, A.Y. Tan, P.C. Chang, H.L. Lee, F.C. Lin, S.J. Yeh, M.C. Fishbein, S.F. Lin, D. Wu, M.S. Wen, and P.S. Chen (2008). **Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure.** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 5(8): 1170-7.

Abstract: BACKGROUND: Heart failure increases autonomic nerve activities and changes intracellular calcium (Ca(i)) dynamics. OBJECTIVE: The purpose of this study was to investigate the hypothesis that abnormal Ca(i) dynamics are responsible for triggered activity in the pulmonary veins (PVs) during acetylcholine infusion in a canine model of heart failure. METHODS: Simultaneous optical mapping of Ca(i) and membrane potential was performed in isolated Langendorff-perfused PV-left atrial (LA) preparations from nine dogs with ventricular pacing-induced heart failure. Mapping was performed at baseline, during acetylcholine (1 micromol/L) infusion (N = 9), and during thapsigargin and ryanodine infusion (N = 6). RESULTS: Acetylcholine abbreviated the action potential. In four tissues, long pauses were followed by elevated diastolic Ca(i), late phase 3 early afterdepolarizations, and atrial fibrillation (AF). The incidence of PV focal discharges during AF was increased by acetylcholine from 2.4 +/- 0.6 beats/s (N = 4) to 6.5 +/- 2.2 beats/s (N = 8; P = .003). PV focal discharge and PV-LA microreentry coexisted in 6 of 9 preparations. The spatial distribution of dominant frequency demonstrated a focal source pattern, with the highest dominant frequency areas colocalized with PV focal discharge sites in 35 (95%) of 37 cholinergic AF episodes (N = 8). Thapsigargin and ryanodine infusion eliminated focal discharges in 6 of 6 preparations and suppressed the inducibility of AF in 4 of 6 preparations. PVs with focal discharge have higher densities of parasympathetic nerves than do PVs without focal discharges (P = .01), and periodic acid-Schiff (PAS)-positive cells were present at the focal discharge sites. CONCLUSION: Ca(i) dynamics are important in promoting triggered activity during acetylcholine infusion in PVs from pacing-induced heart failure. PV focal discharge sites have PAS-positive cells and high densities of parasympathetic nerves.

Descriptors: acetylcholine pharmacology, calcium metabolism, heart failure physiopathology, heart ventricles drug effects, pulmonary veins drug effects, pulmonary veins physiopathology, vasodilator agents pharmacology, acetylcholine administration and dosage, calcium transporting atpases drug effects, cardiac pacing, artificial, dogs, enzyme inhibitors pharmacology, heart failure etiology, models, animal, ryanodine pharmacology, stroke volume, thapsigargin pharmacology, vasodilator agents administration and dosage, left ventricular function.

Christian, T.F., A.H. Aletras, and A.E. Arai (2008). **Estimation of absolute myocardial blood flow during first-pass MR perfusion imaging using a dual-bolus injection technique: comparison to single-bolus injection method.** *Journal of Magnetic Resonance Imaging JMRI* 27(6): 1271-7. ISSN: 1053-1807.

Abstract: PURPOSE: To compare the dual-bolus to single-bolus quantitative first-pass magnetic resonance myocardial perfusion imaging for estimation of absolute myocardial blood flow (MBF). MATERIALS AND METHODS: Dogs had local hyperemia of MBF in the left anterior descending (LAD) coronary artery (intracoronary adenosine). Animals (n = 6) had sequential single- and dual-bolus perfusion studies with microsphere determination of absolute MBF. Perfusion imaging was performed using a saturation-recovery gradient-echo sequence. Absolute MBF was by Fermi function deconvolution and compared to transmural, endocardial, and epicardial microsphere values in the same region of interest (ROI). RESULTS: Signal and contrast were significantly higher for the dual-bolus perfusion images. The correlation with MBF by microspheres was r = 0.94 for the dual-bolus method and r = 0.91 for the single-bolus method. There was no significant difference between MRI and microsphere MBF values for control or hyperemic zones for transmural segments for either technique. When the ROI was reduced to define endocardial and epicardial zones, single-bolus MR first-pass imaging significantly overestimated MBF and had a significantly larger absolute error vs. microspheres when compared to dual-bolus perfusion. CONCLUSION: Both single-bolus and dual-bolus perfusion methods correlate closely with MBF but the signal and contrast of the dual-bolus images are greater. With smaller nontransmural ROIs where signal is reduced, the dual-bolus method appeared to provide slightly more accurate results. 2008 Wiley-Liss, Inc

Descriptors: contrast media administration and dosage, coronary circulation physiology, gadolinium dtpa administration and dosage, image enhancement methods, magnetic resonance angiography methods, blood flow velocity, dogs, microspheres, models, animal, reproducibility of results, time factors.

Chu, Y., Y.C. Wu, Y.C. Chou, H.Y. Chueh, H.P. Liu, J.J. Chu, and P.J. Lin (2004). **Endothelium-dependent relaxation of canine pulmonary artery after prolonged lung graft preservation in university of wisconsin solution: role of l-arginine supplementation**. *Journal of Heart and Lung Transplantation* 23(5): 592-598. ISSN: 1053-2498.

Abstract: Background: The University of Wisconsin (UW) solution has been demonstrated to enhance pulmonary allograft preservation. Endothelial nitric oxide (NO) production has been shown to be significantly impaired after ischemia and reperfusion (I/R) injury. The present experiments aimed to determine the protective effects of pulmonary endothelium-dependent function by using supplemental NO in University of Wisconsin (UW) solution following prolonged lung graft preservation. Methods: Thirty-six healthy mongrel dogs underwent thoracotomy to expose the left lung. In addition to a group given UW solution (n = 4), 100 mumol/liter L-arginine, (n = 7), 100 mumol/liter NG-monomethyl-L-arginine (L-NMMA n = 7) and 1.0 mumol/liter 3-morpholinosydnonimine (SIN-1, n = 18 respectively, were added to UW solution, and infused from the aortic root and pulmonary artery to the pulmonary vein. The perfused lung was then allowed to inflate to its maximum volume for 24-hour oxygenated preservation in each supplemented condition of UW solution at 4degreeC. In the SIN-1 group, the preservation period was further divided into 8 hours

and 16 hours, respectively. Rings of the third-order pulmonary artery of the inflated lung were then suspended in organ chambers to measure isometric force. Results: Endothelium-dependent relaxation (EDR) to acetylcholitie, adenosine diphosphate and sodium fluoride of the pulmonary rings in the L-arginine group was significantly preserved compared with UW-solution-only group. The L-NMMA group showed significant EDR impairment after 24-hour preservation compared with the UW solution group. Similar to the L-arginine group, the SIN-1 group showed significant EDR protection with 8-hour preservation, but not with 24-hour preservation. In contrast, EDR to calcium ionophore A23187 showed no EDR changes after 24-hour preservation in any of the supplemented groups. Conclusions: Supplemental L-arginine in UW solution ameliorates impaired pulmonary EDR following prolonged lung preservation of up to 24 hours.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, respiratory system, respiration, ischemia and reperfusion injury, vascular disease, pathology, prolonged lung graft preservation.

Coxson, P.G., K.M. Brennan, S.E. Taylor, M.K. Huesman, S. Lim, R.H. Huesman, and T.F. Budinger (1996). **Dipyridamole-induced stress-variability in 82rb pet kinetic studies in the anesthetized canine**. *Journal of Nuclear Medicine* 37(5 SUPPL.): 146P. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Descriptors: cardiovascular system, transport and circulation, morphology, meeting abstract, meeting poster, myocardium, rubidium 82 positron emission tomography.

Cremona, G., C.F. Donner, and T.S. Hakim (1997). **Nonlinear behaviour of resistance and compliance in isolated dog lung lobes**. *European Respiratory Journal Supplement* 10(25): 433S-434S. ISSN: 0904-1850.
Descriptors: cardiovascular system, transport and circulation, respiratory system, respiration, pulmonary hemodynamics, meeting abstract.

Ding, C., L. Rao, S.F. Nagueh, and D.S. Khoury (2005). **Dynamic three-dimensional visualization of the left ventricle by intracardiac echo cardiography**. *Ultrasound in Medicine and Biology* 31(1): 15-21. ISSN: 0301-5629.
NAL Call Number: QC244.U4
Descriptors: cardiovascular system, transport and circulation, methods and techniques, intracardiac echocardiography, laboratory techniques, hemodynamics, left ventricular volume, catheterization.

Discigil, B., R.M. King, P.J. Pearson, V.K. Capellini, A.J. Rodrigues, H.V. Schaff, and P.R. Evora (2008). **High-frequency ultrasonic waves cause endothelial dysfunction on canine epicardial coronary arteries.** *Revista Brasileira De Cirurgia Cardiovascular Orgao Oficial Da Sociedade Brasileira De Cirurgia Cardiovascular* 23(2): 190-6.
Abstract: OBJECTIVE: Application of ultrasound energy by an endarterectomy probe can facilitate the removal of atheromatous plaque, but the effect of this procedure on surrounding vessel structure and function is still a matter of experimental investigations. METHODS: To determine whether ultrasound energy impairs the production of nitric oxide or damages

vascular smooth muscle function, isolated canine epicardial coronary artery segments were exposed to either high (25 W) or low (0-10 W) ultrasonic energy outputs, for 15 seconds, using an endarterectomy device prototype. After exposure, segments of epicardial coronary artery were studied in organ chambers. The following drugs were used: adenosine diphosphate (ADP), acetylcholine (Ach) and sodium fluoride (NaF) to study endothelium-dependent relaxation and sodium nitroprusside (SNP) and isoproterenol to evaluate endothelium-independent relaxation. RESULTS: Application of high ultrasonic energy power impaired endothelium-dependent relaxation to ADP (10(-9)-10(-4) M), Ach (10(-9)-10(-4) M) and NaF (0.5-9.5 mM) in epicardial coronary arteries. However, low ultrasound energy output at the tip of the probe did not alter the endothelium-dependent relaxation (either maximal relaxation or EC50) to the same agonists. Vascular smooth muscle relaxation to isoproterenol (10(-9)-10(-5) M) or SNP (10(-9)-10(-6) M) was unaltered following exposure to either low or high ultrasonic energy outputs. CONCLUSION: These experiments currently prove that ultrasonic energy changes endothelial function of epicardial coronary arteries at high power. However, ultrasound does not alter the ability of vascular smooth muscle of canine epicardial coronary arteries to relax.
Descriptors: endothelium, vascular injuries, muscle, smooth, vascular injuries, nitric oxide biosynthesis, ultrasonic therapy adverse effects, ultrasonography, interventional adverse effects, acetylcholine pharmacology, adenosine diphosphate pharmacology, analysis of variance, coronary vessels injuries, coronary vessels metabolism, dogs, endarterectomy methods, endothelium, vascular drug effects, endothelium, vascular physiopathology, isoproterenol pharmacology, models, animal, muscle, smooth, vascular drug effects, muscle, smooth, vascular physiopathology, nitroprusside pharmacology, sodium fluoride pharmacology, ultrasonography, interventional methods, vasodilation drug effects, vasodilation physiology.
Language of Text: Portuguese.

Doi, A., M. Takagi, I. Toda, M. Teragaki, M. Yoshiyama, K. Takeuchi, and J. Yoshikawa (2003). **Real time quantification of low temperature radiofrequency ablation lesion size using phased array intracardiac echocardiography in the canine model: comparison of two dimensional images with pathological lesion characteristics.** *Heart (London)* 89(8): 923-927. ISSN: 1355-6037.
NAL Call Number: RB37.C43
Abstract: Objective: To evaluate the feasibility of quantifying low temperature radiofrequency catheter ablation (RFCA) lesions using a phased array intracardiac echocardiography (ICE) catheter-with better tissue penetration and in a deflectable device-in the canine model. Intervention: Low temperature radiofrequency (RF) energy (50-60degreeC at up to 40 W) was delivered to the left ventricle in 11 beagles for 60 seconds, using an 8 French catheter with a deflectable tip and a 4 mm distal electrode. Main outcome measures: Comparison of the width and depth of RFCA lesions measured by ICE with pathological findings. Results: 33 RF energies were delivered in 11 dogs. 31 lesions (94%) were confirmed at necropsy. 27 of 31 ablation lesions (87%) were detected by ICE. The mean (SD) width and depth of the ICE detected lesions were 10.4 (2.6) mm and 5.7 (1.9) mm, respectively. Pathological findings showed that RFCA lesions consisted of inner and outer layers. Macroscopically, the mean (SD) width and depth of the inner layers were 7.6 (2.3) mm and 3.6 (1.2) mm and those for the whole layers were 10.0 (2.8) mm and 5.3 (1.5) mm, respectively. Microscopi-

cally, the inner and outer layers corresponded to necrotic and oedematous areas, respectively. The ICE detected lesion size had better correlation with the pathological measurements of the whole layers in width (r = 0.911) and in depth (r = 0.756). Conclusion: The real time evaluation of RFCA lesion size using the phased array ICE is feasible, even with a low temperature RF application. However, ICE slightly overestimates RFCA lesion size compared with pathological necrotic lesion size.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, french catheter, medical equipment, intracardiac echocardiography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, radiofrequency catheter ablation, therapeutic and prophylactic techniques, lesion size, tissue penetration.

Dourado, P.M., J.M. Tsutsui, A.C.P. Chagas, W.J. Mathias, J.L. Andrade, and P.L. Da Luz (2003). **The real value of contrast echocardiography in the identification of stunned myocardium in an occlusion-reperfusion dog model.** *FASEB Journal* 17(4-5): Abstract No. 342.10. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, methods and techniques, muscular system, movement and support, veterinary medicine, medical sciences, ischemia, vascular disease, occlusion reperfusion, anterior descending coronary artery occlusion, experimental surgical techniques, laboratory techniques, contrast echocardiography, clinical techniques, diagnostic techniques, electromagnetic flowmeter, medical equipment, real time myocardial contrast echocardiography, diagnostic techniques, reperfusion, clinical techniques, therapeutic and prophylactic techniques, triphenyltetrazolium chloride staining, tcc, imaging and microscopy techniques, necrosis.

Eldstrom, J., D.R. Van Wagoner, and D. Fedida (2004). **Kv1.5 Is highly expressed in canine atrial myocytes.** *Biophysical Journal* 86(1): 533A. ISSN: 0006-3495.
NAL Call Number: 442.8 B5238
Abstract: Canine atria have been used as a model to study atrial fibrillation and the effects of rapid atrial pacing on atrial electrical remodeling. To date, Kv3.1 is thought to be the sole molecular species underlying the atrial-specific, ultra-rapid delayed rectifier K+ current (IKur) in canine atria. Here, using RT-PCR, we have found that Kv1.5 mRNA was highly expressed in canine atrial tissue, while message for Kv3.1 was not. Western analysis detected Kv3.1 only in brain preparations, while Kv1.5 was expressed at high levels in both atrial and ventricular membrane fractions. Confocal imaging clearly demonstrated the presence of Kv1.5 immunostaining in single atrial myocytes. The channel was found at the surface of the myocytes both at intercalated discs and along lateral membranes. Double labeling with a sarcomeric actinin antibody showed co-localization of the channel and actinin proteins where the Z-line met the surface membrane, supporting previous data from rat showing Kv1.5 can be immunoprecipitated with actinin-2. Kv3.1 staining was faintly observable but unchanged after pre-incubation of the antibody with the blocking peptide. We conclude from our results that Kv1.5 but not Kv3.1 is expressed in our canine atrial samples.
Descriptors: cardiovascular system, transport and circulation, membranes, cell biology, atrial fibrillation, heart disease, reverse transcriptase polymerase chain reaction, genetic techniques,

laboratory techniques, atrial electrical remodeling, atrial specific ultra rapid delayed rectifier potassium ion current, rapid atrial pacing.

Eto, M., S. Morita, M. Sugiura, T. Yoshimura, R. Tominaga, and T. Matsuda (2007). **Elastomeric surgical sealant for hemostasis of cardiovascular anastomosis under full heparinization.** *European Journal of Cardio Thoracic Surgery Official Journal of the European Association for Cardio Thoracic Surgery* 32(5): 730-4. ISSN: 1010-7940.
NAL Call Number: RD598
Abstract: PURPOSE: We developed a novel surgical sealant, a viscous diisocyanated prepolymer, applicable to arterial hemostasis. The purpose of this study is to evaluate hemostatic effect of this surgical sealant under heparinized conditions. METHODS: The effectiveness of this sealant was verified by applying it to the end-to-end anastomosis of canine carotid arteries. Five mongrel dogs were used. After a complete heparinization, the carotid arteries were clamped, divided, and end-to-end anastomoses were performed with four simple interrupted sutures. The sealant was coated on the anastomosis. After 5 min the clamps were removed and the hemostatic effect was evaluated. Three dogs were immediately subjected to macroscopic evaluation. Two dogs were subjected to angiography after 3 months and 16 months, respectively. RESULTS: No bleeding occurred in any of the anastomoses immediately after the removal of the clamp. Macroscopic finding revealed no leakage of the sealant into the lumen. Carotid angiography revealed patent anastomoses without stenosis. CONCLUSION: A novel surgical sealant exhibited rapid and potent hemostatic effect on a moisturized tissue under full heparinization.
Descriptors: blood loss, surgical prevention and control, cardiovascular surgical procedures methods, hemostasis, surgical methods, polymers standards, tissue adhesives standards, anastomosis, surgical methods, dogs, hemorrhage prevention and control, models, animal, postoperative hemorrhage prevention and control.

Eto, Y., H. Yamada, Y. Zhang, D.A. Agler, E. Donal, and T.N. Mazgalev (2003). **Effect of ventricular slowing during atrial fibrillation on relationship between cycle length irregularity and mitral annular velocity: a chronic conscious canine model.** *Circulation* 108(17 Supplement): IV-393. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, methods and techniques, atrial fibrillation, heart disease, atrioventricular node vagal stimulation, clinical techniques, therapeutic and prophylactic techniques, right atrial pacing, clinical techniques, tissue doppler echocardiography, diagnostic techniques, r r interval, aortic pulse pressure, arterial pressure, cycle length irregularity, left ventricular ejection fraction, left ventricular systolic function, mitral annular systolic velocity, ventricular rate, ventricular slowing.

Eun, L.Y., E. Arruda, G.J. Ensing, and A. Ludomirsky (2003). **Does cardiac muscle restoration of the left ventricle differ from the right ventricle in the normal canine heart? A passive stress-strain relationship.** *Pediatric Research* 53(4 Part 2): 31A-32A ISSN: 0031-3998.
NAL Call Number: RJ1.P4
Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, cardiac restoration, clinical techniques, therapeutic and prophylactic

techniques, circumferential orientation, force length relationships, longitudinal orientation, passive stress strain relationship, lagrangian, radial orientation, ventricular diastolic function.

Fedorov, V.V., G.G. Beloshapko, A.V. Yushmanova, O.F. Sharifov, and L.V. Rosenshtraukh (2003). **Effects of a new class iii antiarrhythmic drug nibentan in a canine model of spontaneous atrial fibrillation.** *European Heart Journal* 24(Abstract Supplement): 391. ISSN: 0195-668X.
Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial premature depolarization, heart disease, prevention and control, reentrant arrhythmia, heart disease, prevention and control, spontaneous atrial fibrillation, heart disease, drug therapy, atrial electrical stimulation, clinical techniques, ik potassium current, atrial effective refractory period, basic cycle length, conduction velocity.

Fedorov, V.V., O.P. Trifonova, A.V. Glukhov, G.G. Beloshapko, A.V. Iushmanova, and L.V. Rozenshtraukh (2004). **Vliianie vnutripredserdnogo davleniia na kharakter vozniknoveniia vagotonicheskoi fibrilliatsii predserdii u sobak.** *Kardiologiia* 44(12): 51-63. ISSN: 0022-9040.
Abstract: Atrial fibrillation (AF) frequently occurred under conditions associated with atrial dilatation (stretch) or vagal hyperactivity. To study possible role of atrial stretch in spontaneous initiation of vagal AF we compared changes of right atrial pressure (RAP) and activation patterns during AF beginning. In anesthetized open-chest dogs (n=45) AF was induced by stimulation of vagal nerves (VS) (30-60 Hz, 5-10 s train). VS resulted in sinus node arrest (4.7+/-0.7 sec) with subsequent AF initiation in 153 of 229 cases. In 41% of cases of AF initiation the first atrial wave (A(1)) was closely related to ventricular activation (V) with V-A(1) interval of 94+/-5 ms (<<ventricle-dependent>> AF). This ventricular excitation induced acute short increase of RAP from 6.6.+/-0.6 to 12.9+/-1.1 mmHg (p<0.00l). Whereas other cases of AF initiation (59%) had no relation to ventricular activation (A(1)-V interval of 1382+/-173 ms) (<<ventricle-independent>> AF). Atrial activation mapping (224 unipolar electrodes) showed that interval A(1)-A(2) of <<ventricle-dependent>> AF was significantly shorter than of <<ventricle-independent>>. These data indicate that atrial stretch induced by elevation of RAP may facilitate the induction of AF but do not play a significant role in the mechanism of spontaneous AF initiation in this animal model.
Descriptors: animal model, open chest dogs, atrial fibrillation, vagal hyperactivity, atrial stretch.
Language of Text: Russian

Fenelon, G., R.K. Shepard, and B.S. Stambler (2003). **Focal origin of atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure.** *Journal of Cardiovascular Electrophysiology* 14(10): 1093-1102. ISSN: 1045-3873.
Abstract: Introduction: Dogs with rapid ventricular pacing-induced congestive heart failure (CHF) have inducible atrial tachycardia (AT), with a mechanism consistent with delayed afterdepolarization-mediated triggered activity. We assessed the hypothesis that AT has a focal origin. Methods and Results: Twenty-one CHF dogs undergoing 3 to 4 weeks of ventricular pacing at 235 beats/min were studied. Biatrial epicardial mapping of 20 sustained AT episodes (cycle length (CL), 175+-53 msec) in 5 dogs revealed an area of earliest activation in the right atrial (RA) free wall (13 episodes), RA appendage (4 episodes), or between

the pulmonary veins (3 episodes). Total epicardial activation time during AT (73+-19 msec) was similar to that during sinus rhythm (72+-13 msec) and on average was <50% of the AT CL. Higher-density mapping of the RA free wall during 30 sustained AT episodes (163+-55 msec) in 9 dogs identified a site of earliest activation along the sulcus terminalis most frequently as a stable, focal activation pattern from a single site. Endocardial mapping of 49 sustained AT episodes (156+-27 msec) in 10 dogs revealed multiple sites of AT origin arising along the crista terminalis and pulmonary veins. Right and left ATs were terminated with discrete radiofrequency ablation, but other ATs remained inducible. A rapid, left AT generating an ECG pattern of atrial fibrillation was ablated inside the pulmonary vein. Conclusion: AT induced in this CHF model after 3 to 4 weeks of rapid ventricular pacing has an activation pattern consistent with a focal origin. Sites of earliest activation are distributed predominately along the crista terminalis and within or near the pulmonary veins.
Descriptors: cardiovascular system, transport and circulation, veterinary medicine, medical sciences, atrial tachycardia, heart disease, congestive heart failure, rapid ventricular pacing, induced heart failure, heart disease, biatrial epicardial mapping, clinical techniques, ventricular pacing, clinical techniques, sinus rhythm.

Forrest, M.J., D. Bloomfield, R.J. Briscoe, P.N. Brown, A.M. Cumiskey, J. Ehrhart, J.C. Hershey, W.J. Keller, X. Ma, H.E. McPherson, E. Messina, L.B. Peterson, W. Sharif Rodriguez, P.K. Siegl, P.J. Sinclair, C.P. Sparrow, A.S. Stevenson, S.Y. Sun, C. Tsai, H. Vargas, M.3. Walker, S.H. West, V. White, and R.F. Woltmann (2008). **Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone.** *British Journal of Pharmacology* 154(7): 1465-73. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: BACKGROUND AND PURPOSE: Inhibition of cholesteryl ester transfer protein (CETP) with torcetrapib in humans increases plasma high density lipoprotein (HDL) cholesterol levels but is associated with increased blood pressure. In a phase 3 clinical study, evaluating the effects of torcetrapib in atherosclerosis, there was an excess of deaths and adverse cardiovascular events in patients taking torcetrapib. The studies reported herein sought to evaluate off-target effects of torcetrapib. EXPERIMENTAL APPROACH: Cardiovascular effects of the CETP inhibitors torcetrapib and anacetrapib were evaluated in animal models. KEY RESULTS: Torcetrapib evoked an acute increase in blood pressure in all species evaluated whereas no increase was observed with anacetrapib. The pressor effect of torcetrapib was not diminished in the presence of adrenoceptor, angiotensin II or endothelin receptor antagonists. Torcetrapib did not have a contractile effect on vascular smooth muscle suggesting its effects in vivo are via the release of a secondary mediator. Treatment with torcetrapib was associated with an increase in plasma levels of aldosterone and corticosterone and, in vitro, was shown to release aldosterone from adrenocortical cells. Increased adrenal steroid levels were not observed with anacetrapib. Inhibition of adrenal steroid synthesis did not inhibit the pressor response to torcetrapib whereas adrenalectomy prevented the ability of torcetrapib to increase blood pressure in rats. CONCLUSIONS AND IMPLICATIONS: Torcetrapib evoked an acute increase in blood pressure and an acute increase in plasma adrenal steroids. The acute pressor response to torcetrapib was not mediated by adrenal steroids but was dependent on intact adrenal glands.
Descriptors: blood pressure drug effects, cholesterol ester transfer proteins antagonists and

inhibitors, oxazolidinones toxicity, quinolines toxicity, adrenal cortex cytology, adrenal cortex drug effects, aldosterone blood, anticholesteremic agents toxicity, corticosterone blood, dogs, drug evaluation, preclinical, macaca mulatta, mice, mice, inbred c57bl, models, animal, muscle, smooth, vascular drug effects, muscle, smooth, vascular metabolism, rats, rats, sprague dawley, species specificity.
Notes: Comment In: Br J Pharmacol. 2008 Aug;154(7):1379-81.

Freitas, C.F., R. Faro, D. Dragosavac, M. Clozel, G. De Nucci, and E. Antunes (2004). **Role of endothelin-1 and thromboxane a2 in the pulmonary hypertension induced by heparin-protamine interaction in anesthetized dogs.** *Journal of Cardiovascular Pharmacology* 43(1): 106-112. ISSN: 0160-2446.
Abstract: This study aimed to study the role of thromboxane A2 (TXA2) and endothelin-1 (ET-1) in the pulmonary hypertension induced by interaction of heparin-protamine in anesthetized dogs. The effect of inhaled nitric oxide (NO) was also investigated in this model. Dogs were anesthetized and instrumented for acquisition of mean arterial blood pressure, mean arterial pulmonary pressure (MPAP), and pulmonary pressure gradient (PPG). Cardiac index (CI), heart rate, and index of systemic vascular resistance were also obtained. Intravenous administration of heparin (500 IU/kg) 3 minutes before protamine (10 mg/kg) caused marked pulmonary hypertension, as evaluated by the increase in MPAP and PPG. This was accompanied by systemic hypotension, CI decrease, and tachycardia. Indomethacin (10 mg/kg), dazoxiben (10 mg/kg), or tezosentan (10-mg/kg bolus plus 10-mg/kg/h infusion) significantly reduced the increase in MPAP and PPG, but had no effect on the systemic hypotension. Similar results were obtained with inhaled NO (3 ppm). Plasma TXB2 levels were markedly elevated during the pulmonary hypertension, and this was abolished in indomethacin-treated dogs. Our study shows that interaction of heparin-protamine in anesthetized dogs lead to TXA2- and ET-1-mediated pulmonary hypertension. Drugs that interfere with the synthesis of these mediators as well as inhaled NO may be of beneficial value to control this disorder.
Descriptors: cardiovascular system, transport and circulation, pharmacology, pulmonary hypertension, vascular disease, tachycardia, heart disease, cardiac index, heart rate, heparin protamine interaction, mean arterial blood pressure, mean arterial pulmonary pressure, pulmonary pressure gradient, systemic vascular resistance index.

Fujii, Y., K. Orito, M. Muto, and Y. Wakao (2007). **Modulation of the tissue reninangiotensin-aldosterone system in dogs with chronic mild regurgitation through the mitral valve.** *American Journal of Veterinary Research* 68(10): 1045-50. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Abstract: OBJECTIVE: To investigate whether the tissue and plasma renin-angiotensin-aldosterone system (RAAS) is activated in dogs with mild regurgitation through the mitral valve and determine the contribution of chymase and angiotensin-converting enzyme (ACE) to the activation of the RAAS and potential production of angiotensin II during the chronic stage of mild mitral valve regurgitation. ANIMALS: 5 Beagles with experimentally induced mild mitral valve regurgitation and 6 clinically normal (control) Beagles. PROCEDURES: Tissue ACE and chymase-like activities and plasma RAAS were measured and the RAAS evaluated approximately 1,000 days after experimental induction of mitral valve regurgita-

tion in the 5 dogs. RESULTS: Dogs with experimentally induced mitral valve regurgitation did not have clinical signs of the condition, although echocardiography revealed substantial eccentric hyper- trophy. On the basis of these findings, dogs with mitral valve regurgitation were classified as International Small Animal Cardiac Health Council class Ib. Plasma activity of renin and plasma concentrations of angiotensin I, angiotensin II, and aldosterone were not significantly different between dogs with mitral valve regurgitation and clinically normal dogs. Tissue ACE activity was significantly increased and chymase-like activity significantly decreased in dogs with mitral valve regurgitation, compared with values in clinically normal dogs. CONCLUSIONS AND CLINICAL RELEVANCE: The tissue RAAS was modulated without changes in the plasma RAAS in dogs with mild mitral valve regurgitation during the chronic stage of the condition. An ACE-dependent pathway may be a major route for production of angiotensin II during this stage of the condition.
Descriptors: dog diseases physiopathology, mitral valve insufficiency veterinary, renin angiotensin system physiology, chronic disease, chymases metabolism, dog diseases enzymology, dogs, mitral valve insufficiency enzymology, mitral valve insufficiency physiopathology, models, animal, peptidyl dipeptidase a metabolism, reference values.

Gallegos, R.P., C. Swingen, N.J. Xu, X. Wang, R. Bianco, M. Jerosch Herold, and R.M. Bolman (2004). **Infarct extent by mri corelates with peak serum troponin level in the canine model**. *Journal of Surgical Research* 120(2): 266-271. ISSN: 0022-4804.
Descriptors: Serum Troponin I, biochemistry and molecular biophysics, cardiovascular system, diagnosis, myocardial infarction, heart disease, vascular disease, magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, blood immunoassay, bioassay techniques, coronary artery ligation, therapeutic and prophylactic techniques, electrocardiography, thoracotomy, infarct size.

Garrido, M.J., M.R. Williams, A. Kherani, D.W. Vigilance, D. Parish, H. Hermoni, Y. Naka, C.R.J. Smith, M.C. Oz, and M. Argenziano (2003). **Linear ethanol jet injection for surgical treatment of atrial fibrillation: canine survival study.** *Journal of the American College of Cardiology* 41(6 Supplement A): 92A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, atrial fibrillation, heart disease, therapy, beating ethanol linear jet injection, laboratory techniques, therapeutic and prophylactic techniques.

Ge Lei , Wei Meng , Yao Rui Ming , and Et Al (2003). **Therapeutic angiogenesis with intramyocardial administration of basic fibroblast growth factor in a canine model of acute myocardial infarction.** *Zhonghua Xinxueguanbing Zazhi* 31(6): 452-455. ISSN: 0253-3758.
Abstract: Objective: To evaluate the effects of intramyocardial administration of basic fibroblast growth factor (bFGF) on myocardial blood flow and angiogenesis in a canine acute myocardial infarction model. Methods: Myocardial infarction was induced in 17 dogs by ligation of the first, second diagonal branches of left anterior descending (LAD) and the first, second obtuse marginal branches of LCX. 200 mug of human recombinant bFGF in 0.2 ml of saline was injected into the infarct border zone 20 minutes after coronary occlusion in 9 dogs, whereas 200 mul saline was used in 8 control dogs. Myocardial blood flow, which

was expressed as percentage of normal, was determined with non-radioactive colored microspheres before and immediately after coronary ligation, 3 hours, 7 days and 28 days after treatment. Angiogenesis was determined at the end of the whole study. Results: Compared with control group, treatment with 200 mug bFGF significantly increased the epicardial blood flow in the infracted zone ((36.40+-2.04)% vs (32.32+-3.07)% 3 hours after coronary ligation, P<0.05; (56.30+-3.49)% vs (35.68+-1.62)% 7 days after coronary ligation, P<0.01; and (70.62+-3.17)% vs (46.20+-2.58)% 28 days after coronary ligation, P<0.01, respectively). bFGF also significantly increased the epicardial blood flow in the border zone ((68.06+-2.69)% vs (53.94+-2.27)% 7 days after coronary ligation, P<0.01; (79.74+-4.61)% vs (61.84+-4.52)% 28 days after coronary ligation, P<0.01, respectively). bFGF increased the vessel density in the infarcted zone (7.24+-1.89 vessels/mm2 vs 4.07+-1.89 vessels/mm2, P<0.05) and infarcted border zone (14.48+-4.69 vessels/mm2 vs 8.15+-3.43 vessels/mm2, P<0.05). Conclusion: The current study shows that intramyocardial administration of bFGF increases the regional myocardial blood flow and promotes myocardial collateral vessel formation in the canine acute myocardial infarction model.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, acute myocardial infarction, heart disease, vascular disease, coronary occlusion, coronary ligation, experimental surgical techniques, laboratory techniques, therapeutic angiogenesis, clinical techniques, therapeutic and prophylactic techniques.
Language of Text: Chinese.

Ge, Z.D., J. Moore, G.J. Gross, and J.A. Auchampach (2003). **The a3 adenosine receptor agonist ib-meca reduces myocardial infarct size in anesthetized dogs.** *FASEB Journal* 17(4-5): Abstract No. 151.5. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, myocardial infarction, heart disease, vascular disease, left anterior descending artery occlusion, experimental surgical techniques, laboratory techniques, coronary blood flow.

Ghiassi, S., Y.S. Sun, V.B. Kim, C.M. Scott, L.W. Nifong, M.F. Rotondo, and W.R.J. Chitwood (2004). **Methylene blue enhancement of resuscitation after refractory hemorrhagic shock**. *Journal of Trauma Injury Infection and Critical Care* 57(3): 515-521. ISSN: 1079-6061.
Abstract: Background: Methylene blue has been used to treat hypovolemic states. This study evaluated prehospital resuscitation after refractory hemorrhagic shock with a combination of methylene blue and limited-volume lactated Ringer's solution. Methods: After blood loss to a mean arterial pressure of 50 mm Hg in canines, refractory hemorrhagic shock was defined as minimal hemodynamic response to phenylephrine. Differential protocols included no treatment (control), methylene blue bolus, limited-volume lactated Ringer's solution, and combined methylene blue/lactated Ringer's solution therapies. Hemodynamic parameters were collected at baseline, during shock, during refractory hemorrhagic shock, and 30, 60, 90, and 120 minutes after treatment. Radiolabeled microspheres were used to measure end-organ perfusion and oxygen delivery. Results: Methylene blue/lactated Ringer's resuscitation improved prehospital survival (p 0.05), mean arterial pressure and cardiac output (p 0.05),

vital end-organ blood flow and oxygen delivery (p 0.05), and decreased serum lactate levels (p 0.05), as compared with the methylene blue and lactated Ringer's single therapies. Conclusions: Resuscitation after refractory hemorrhagic shock using a combination of methylene blue and limited-volume lactated Ringer's solution improves prehospital survival and hemodynamic stability and reduces ischemic damage in an acute setting. This form of therapy has been proved useful as a temporizing measure for resuscitation after refractory hemorrhagic shock in a canine model and warrants further study for its application to the hemorrhagic trauma patient.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, nervous system, neural coordination, hemorrhagic shock, nervous system disease, vascular disease, radiolabeling, laboratory techniques, arterial pressure, cardiac output, end organ blood flow.

Glaus, T.M., M. Hassig, C. Baumgartner, and C.E. Reusch (2003). **Pulmonary hypertension induced in dogs by hypoxia at different high-altitude levels.** *Veterinary Research Communications* 27(8): 661-670. ISSN: 0165-7380.

NAL Call Number: SF601 .V38

Abstract: Chronic natural hypoxia at 2300 in altitude induces mild pulmonary hypertension (PH) in healthy dogs. The influence of more severe hypoxia on the same group of dogs was evaluated by re-examining such dogs at 3500 m, after they had regularly exercised at this altitude level for half a year. Despite severe hypoxaemia at 3500 in (PaO2 52+-5 mmHg), none of the dogs developed erythrocytosis, and their PCV at 3500 in (48%+-4%) did not differ from that at 2300 in (49%+-40%). There was a tendency towards an elevated systemic BP, with a significant increase in diastolic BP (105+-13 mmHg at 3500 m versus 98+-17 at 2300 m). Tricuspid regurgitation (TR) was detected in 7 dogs at 3500 m compared to 8 dogs at 2300 m. The mean TR Vmax was significantly higher at 3500 m, and all 7 dogs had systolic PH at 3500 in (33.6-54.8 mmHg), when PH was defined as TR Vmax gtoreq2.8 m/s, i.e. a peak pressure gradient >30 mmHg. Hence, in dogs, increasing altitude and the concomitant hypoxia result in a progressively more pronounced PH and an elevated systemic BP. Intermittent severe hypoxaemia of around 50 mmHg may not cause erythrocytosis in healthy dogs, even over a prolonged period.

Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, erythrocytosis, polycythemia, pulmonary hypertension, vascular disease, tricuspid regurgitation, heart disease, blood pressure, chronic natural hypoxia, high altitude, packed cell volume.

Grover, G.J., D.E. Burkett, C.S. Parham, R.J. Scalese, and K.K. Sadanaga (2003). **Protective effect of mitochondrial katp activation in an isolated gracilis model of ischemia and reperfusion in dogs.** *Journal of Cardiovascular Pharmacology* 42(6): 790-792. ISSN: 0160-2446.

Abstract: Adenosine triphosphate-sensitive potassium channel (KATP) openers protect ischemic myocardium by direct protection of cardiac myocytes, which is thought to be a result of activation of mitochondrial KATP (mKATP). KATP is expressed in skeletal muscle, and the purpose of this study was to determine the effect of the mKATP opener BMS-191095 on infarct size in an isolated gracilis model of ischemia and reperfusion in dogs. The right and left gracilis muscles were isolated in anesthetized dogs except for the artery and vein sup-

plying these muscles (pedicle). BMS-191095 (0.4 mg) or vehicle were infused directly into the artery supplying each gracilis muscle (each animal had one drug-treated and one vehicle-treated muscle). The pedicle was completely occluded for 5 hours followed by 48 hours of reperfusion, after which infarct size was determined. In the vehicle-treated gracilis muscles, significant necrosis was observed (82%+-3% of gracilis muscle). BMS-191095 significantly reduced the infarct size in the contralateral gracilis muscle (55%+-6%). Reflow into the gracilis muscle was significantly greater in BMS-191095-treated muscles. BMS-191095 appears to reduce damage in ischemic/reperfused skeletal muscle, suggesting that mKATP activation is an important protective mechanism in this tissue.

Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, pharmacology, ischemia, vascular disease, ischemia reperfusion injury, myocardial ischemia, heart disease, infarct size, isolated gracilis model.

Grundfest, W.S., J. Val Mejias, E. Monnet, B.P. Knight, S. Nazarian, R.D. Berger, T.B.J. Ferguson, M.M. Roden, D. Amundson, J. Hanlin, and L. Blankenship (2007). **Real-time percutaneous optical imaging of anatomical structures in the heart through blood using a catheter-based infrared imaging system.** *Seminars in Thoracic and Cardiovascular Surgery* 19(4): 336-41. ISSN: 1043-0679.

Abstract: The ability to optically image structures and instrumentation within the heart during procedures is limited by the presence of blood in the field. The goal of our research was to design, develop, and evaluate technology for a catheter-based optical imaging system that enables intracardiac and intravascular visualization in real time through blood. Based on Mie optical scattering theory, imaging through blood using infrared light was theoretically feasible, but scattering in the near-infrared wavelengths (1100 to 1300 nm) generated substantial noise in the image despite relatively low absorption. Using illumination between 1550 and 1650 nm provided better images, as the effect of scattering is less while the effect of absorption is greater. Absorption losses can be overcome by increasing light intensity. Infrared (IR) transmitting endoscopes were constructed using novel flexible illumination and imaging bundles. Endoscope designs, all 7.5 Fr. in outer diameter, were used to obtain images of the coronary sinus, tricuspid valve, and great vessels in 25 pigs, 16 dogs, 1 calf, and 1 sheep. Imaging was successful in all 43 animals, but the coronary sinus was not always visualizable. After obtaining FDA 510(k) approval, the device was used to acquire images in 50 patients during placement of electrophysiologic leads via right heart catheterization. Clinical experience demonstrates successful visualization in the heart in 45 patients, although coronary sinus images were obtained only in 39 patients. High heart rates, large dilated hearts, and problems with catheter design prevented visualization in all patients. On occasion, it was possible to visualize the tricuspid valve. Infrared endoscopy allows for visualization of intimal surfaces of blood vessels, cardiac chambers, and valves through flowing blood. While technical challenges remain, the feasibility of the approach has been demonstrated.

Descriptors: angioscopy methods, heart anatomy and histology, heart catheterization instrumentation, infrared rays, optics and photonics, cattle, diagnostic imaging, dogs, feasibility studies, heart physiopathology, heart catheterization methods, models, animal, sheep, swine, time factors.

Gu, W., D. Weihrauch, K. Tanaka, J.P. Tessmer, P.S. Pagel, J.R. Kersten, W.M. Chilian, and D.C. Warltier (2003). **Reactive oxygen species are critical mediators of coronary collateral development in a canine model.** *American Journal of Physiology* 285(4 Part 2): H1582-H1589. ISSN: 0002-9513.

NAL Call Number: 447.8 Am3

Abstract: Recent evidence suggests that reactive oxygen species (ROS) promote proliferation and migration of vascular smooth muscle (VSMC) and endothelial cells (EC). We tested the hypothesis that ROS serve as crucial messengers during coronary collateral development. Dogs were subjected to brief (2 min), repetitive coronary artery occlusions (1/h, 8/day, 21 day duration) in the absence (occlusion, n=8) or presence of N-acetylcysteine (NAC) (occlusion+NAC, n=8). A sham group (n=8) was instrumented identically but received no occlusions. In separate experiments, ROS generation after a single 2-min coronary artery occlusion was assessed with dihydroethidium fluorescence. Coronary collateral blood flow (expressed as a percentage of normal zone flow) was significantly increased (71+-7%) in occlusion dogs after 21 days but remained unchanged (13+-3%) in sham dogs. Treatment with NAC attenuated increases in collateral blood flow (28+-8%). Brief coronary artery occlusion and reperfusion caused ROS production (256+-33% of baseline values), which was abolished with NAC (104+-12%). Myocardial interstitial fluid produced tube formation and proliferation of VSMC and EC in occlusion but not in NAC-treated or sham dogs. The results indicate that ROS are critical for the development of the coronary collateral circulation.

Descriptors: cardiovascular system, transport and circulation, coronary artery occlusion, heart disease, vascular disease, coronary collateral blood flow.

Guan, D.W., X.G. Zhang, R. Zhao, B. Lu, Y. Han, Z.H. Hou, and J.T. Jia (2007). **Diverse morphological lesions and serious arrhythmias with hemodynamic insults occur in the early myocardial contusion due to blunt impact in dogs.** *Forensic Science International* 166(1): 49-57. ISSN: 0379-0738.

NAL Call Number: RA1001

Abstract: To investigate the morphology and hemodynamics of the early myocardial contusion, an animal model of cardiac contusion was established by impact to the precordial region at sternum at velocity of 10.0m/s with a mechanical elastic-cord propelled impactor in 19 dogs. The electrocardiogram and both the left and right intra-ventricular pressures were recorded continuously throughout the experiment. Histological and immunohistochemical examinations of myoglobin, creatine kinase-MB and fibrinogen were conducted. At the moment of impact, abrupt over-pressures within the left and right ventricles occurred with concomitant serious arrhythmias followed by variety of cardiac conduction disorders and depressed left and right ventricular systolic pressures during the observation times. Histologically, lesions of myocardial contusions were identified at subepicardial, myocardial or subendocardial layer as interstitial hemorrhage, disruption or coagulative necrosis as well as contraction band necrosis of the muscle fibers, which might be categorized into the hemorrhagic, necrotized and mixed forms. The three forms of lesions were found to exist independently, or co-existed in a heart. However, severity of the lesions varied greatly with different parts even within a heart. Intravascular thromboses were occasionally discovered post-impact. Immunohistochemically, loss of myoglobin and creatine kinase-MB from

cardiac cells, and accumulation of fibrinogen at the cell membranes were detected 5min post-impact. The intracellular accumulation of fibrinogen increased with extension of post-impact intervals. Our results indicate that diverse morphological lesions concomitant with hemodynamic compromise and serious, even fatal arrhythmias occur in the early myocardial contusion, and intravascular thromboses are occasionally produced, suggesting that traumatic myocardial ischemic lesion may be induced due to blunt impact to the precordial region.
Descriptors: arrhythmias, cardiac physiopathology, heart injuries pathology, wounds, nonpenetrating pathology, dogs, electrocardiography, heart injuries physiopathology, immunohistochemistry, models, animal, ventricular pressure, wounds, nonpenetrating physiopathology.

Guccione, J.M., K.D. Costa, and A.D. Mcculloch (1995). **Finite element stress analysis of left ventricular mechanics in the beating dog heart**. *Journal of Biomechanics* 28(10): 1167-1177. ISSN: 0021-9290.
NAL Call Number: TA166.J6
Abstract: A three-dimensional finite element model was used to explore whether or not transmural distributions of end-diastolic and end-systolic fiber stress are uniform from the apex to the base of the canine left ventricular wall. An elastance model for active fiber stress was incorporated in an axisymmetric model that accurately represented the geometry and fiber angle distribution of the anterior free wall. The nonlinear constitutive equation for the resting myocardium was transversely isotropic with respect to the 4.6 kPa at the apex, and 3.3 kPa at the base. Transmural fiber stress differences at end-systole (14 kPa) were relatively small in regions from the base to the midventricle (13-22 kPa), but were larger between within or very close to one standard deviation of published measurements through the midanterior left ventricular free wall of the passive canine heart (Omens et al., Am. J. Physiol. 261, H918-H928 (1991)). End-systolic in-plane normal and shear strains also agreed closely with published experimental measurements in the beating dog heart (Waldman et al., Circ. Res. 63, 550-562 (1988)). The results indicate that, unlike in the midventricle region that has been studied most fully, there may be significant regional non-homogeneity of fiber stress in the normal left ventricle associated with regional variations in shape and fiber angle.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, mathematical biology, computational biology, models and simulations, mathematical model, myocardium, myofiber stress, systole.

Guo Zhi Bin , Li Qing , Cao Hong Yu , and Xu Zhi (2003). **Comparative study of propafenone and procainamide on canine ischemic ventricular tachyarrhythmias.** *Zhongguo Yaolixue Yu Dulixue Zazhi* 17(5): 360-365. ISSN: 1000-3002.
Abstract: AIM: To observe the electrophysiologic effects of propafenone (Prop) on canine ischemic ventricular tachyarrhythmias and compared with those of procainamide (PA), so as to evaluate the effect and mechanism of Prop on ischemic ventricular tachyarrhythmias. METHODS: A canine ischemic ventricular tachyarrhythmia model was established by the left anterior descending coronary artery occlusion for 2 h and reperfusion. Five to eight days later, open-chest dogs were given programmed electrical stimulation (PES), and electrophysiologic data were measured by electrocardiogram (ECG). RESULTS: Both Prop and

PA distinctly lengthened the QTc interval (P<0.01) and effective refractory period (ERP) of normal and ischemic ventricular myocardium respectively (P<0.01), decreased the dispersion of ERP in ischemic myocardium and in left ventricle (P<0.01), and increased the diastolic excitability threshold of normal and ischemic ventricular myocardium remarkably (P<0.01). Prop and PA effectively prevented PES- or ischemia-induced ventricular tachycardia or ventricular fibrillation (P<0.05, or P<0.01). CONCLUSION: The canine model is a worthy and reliable one. Prop and PA may be effective in preventing the onset of ventricular tachycardia or ventricular fibrillation after myocardial ischemic damage. The antiarrhythmic effects of both drugs are similar.

Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemic ventricular tachyarrhythmia, heart disease, myocardial infarction, heart disease, vascular disease, ventricular fibrillation, ventricular tachycardia, electrocardiography, clinical techniques, diagnostic techniques, programmed electrical stimulation, experimental surgical techniques, laboratory techniques, qtc interval, comparative study, diastolic excitability threshold, disease onset, disease prevention, effective refractory period, electrophysiologic data.

Hainsworth, R., O.A. Sofola, A.J.P. Knill, and M.J. Drinkhill (2003). **Influence of dietary salt intake on the response of isolated perfused mesenteric veins of the dog to vasoactive agents.** *American Journal of Hypertension* 16(1): 6-10. ISSN: 0895-7061.

NAL Call Number: RC685.H8

Abstract: Background: Previous work has established that a high dietary salt intake results in enhanced arterial vasoconstrictor responses to stimulation with agonists. This investigation was designed to investigate the effects of dietary salt on the responses of isolated capacitance vessels (third order mesenteric veins). Methods: Dogs were fed diets containing low, intermediate, and high levels of dietary salt (0.4, 3.0, and 6.0 mmol kg/day). The animals were killed, and lengths of mesenteric vein were mounted in a perfusion myograph with changes in lumenal diameter measured using a video tracking device. Responses to cumulative doses of norepinephrine (NE) and acetylcholine (Ach) were then determined. Results: The vasoconstrictor responses to NE were greater in the veins from dogs on a high salt diet. Acetylcholine also caused venoconstriction that also was greater in the high salt group of animals. Responses to Ach were unaffected by Nomega-nitro-L-arginine methyl ester but were abolished by atropine. Conclusions: These results indicate that mesenteric veins from dogs fed a high salt diet constrict more powerfully in response to agonists, which could contribute to the hypertensive effects of high intakes of dietary salt.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, nutrition.

Hamann, J.J., J.B. Buckwalter, and P.S. Clifford (2004). **Vasodilatation is obligatory for contraction-induced hyperaemia in canine skeletal muscle**. *Journal of Physiology (Oxford)* 557(3): 1013-1020. ISSN: 0022-3751.

NAL Call Number: 447.8 J82

Abstract: There is a rapid increase in blood flow to active skeletal muscle with the onset of exercise, but the mechanism(s) eliciting this increase remains elusive. We hypothesized that the rapid increase in blood flow to active skeletal muscle with the onset of exercise is attributable to vasodilatation as a consequence of smooth muscle hyperpolarization. To test

this hypothesis we examined the blood flow response to a brief tetanic contraction in which potassium (K+) was infused intra-arterially to elevate the (K+)o and clamp the smooth muscle membrane potential within the skeletal muscle vascular bed. In six anaesthetized beagle dogs control contractions increased hindlimb blood flow by 97 +/- 14 ml min-1. During K+ infusion the hyperaemic response to contraction was 8 +/- 3 ml min-1. Since the hindlimb blood flow was reduced during K+ infusion, a similar reduction in baseline blood flow was produced with phenylephrine infusion. During phenylephrine infusion the hyperaemic response to contraction was preserved (89 +/- 23 ml min-1). Recovery contractions performed after the discontinuation of the K+ infusion elicited blood flow responses similar to control (100 +/- 11 ml min-1). In a separate experimental protocol using the isolated gastrocnemius muscle of mongrel dogs (n = 6) K+ infusion did not alter force production by the skeletal muscle. Our data indicate that in the absence of vasodilatation, there is virtually no change in blood flow. One implication of this finding is that the muscle pump cannot be responsible for the initial contraction-induced hyperaemia. We conclude that the increase in blood flow immediately following a single muscle contraction is due to vasodilatation, presumably as a consequence of smooth muscle hyperpolarization.
Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, contraction induced hyperemia, metabolic disease, blood flow response, hindlimb blood flow, recovery contractions, smooth muscle membrane potential, vasodilatation.

Hashimoto, N., I. Takeyoshi, H. Tsutsumi, Y. Sunose, M. Tokumine, O. Totsuka, S. Ohwada, K. Matsumoto, and Y. Morishita (2004). **Effects of a bradykinin b2 receptor antagonist on ischemia-reperfusion injury in a canine lung transplantation model**. *Journal of Heart and Lung Transplantation* 23(5): 606-613. ISSN: 1053-2498.
Abstract: Background: This study investigated the effects of a bradykinin B, receptor antagonist, FR173657 (FR), on ischemia-reperfusion (I/R) injury in a canine lung transplantation model. Methods: Eighteen pairs of weight-matched dogs were randomly divided into 3 groups. Six pairs were assigned to the FR(D+R) group, in which FR (100 nmol/kg/h) was administered to the transplant donor continuously beginning 30 minutes before ischemia until the onset of ischemia, and FR was administered to the transplant recipient beginning 30 minutes before reperfusion and continuing for 2 hours after reperfusion. Another 6 pairs of dogs were assigned to the FR(R) group, in which FR was administered only to the recipient in the same manner as in the FR(D + R) group. The other pairs were assigned to the control group, in which vehicle alone was administered. Orthotopic left lung transplantation was performed after 12-hour cold storage in Euro-Collins solution. Fifteen minutes after reperfusion, the right pulmonary artery and the right stem bronchus were ligated. The animals were measured for 4 hours after reperfusion for left pulmonary vascular resistance (L-PVR), cardiac output (CO), arterial oxygen pressure (Pao2) and alveolar-arterial oxygen pressure difference (A-aDo2). Lung specimens were harvested for measurement of the wet-to-dry lung weight ratio (WDR), histopathologic studies and polymorphonuclear neutrophil (PMN) count. Results: Compared with the control group, Pao2, A-aDo2, L-PVR and CO were all significantly ($p < 0.05$) improved and WDR significantly ($p < 0.05$) lower in both the FR(D+R) and FR(R) groups. Moreover, in the FR-treatcd groups, histologic tissue edema was mild, and PMN infiltration was significantly ($p < 0.05$) reduced. Conclusions: The bra-

dykinin B, receptor antagonist, FR173657, ameliorates I/R injury in lung grafts, indicating that protection of lung grafts can be achieved by the administration of FR solely to the transplant.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, ischemia reperfusion injury, injury, vascular disease, pathology, histopathologic study, histology and cytology techniques, laboratory techniques, lung transplantation, clinical techniques, therapeutic and prophylactic techniques, orthotopic left lung transplantation, alveolar arterial oxygen pressure difference, arterial oxygen pressure, cardiac output, left pulmonary vascular resistance, wet to dry lung weight ratio.

Hatada, K., L.M. Riou, M. Ruiz, R.L. Lima, A.R. Goode, D.D. Watson, G.A. Beller, and D.K. Glover (2003). **Comparison between the myocardial uptake of 99mtcn-dbodc5 and 201ti during vasodilator stress in a canine model of a critical coronary stenosis.** *Journal of the American College of Cardiology* 41(6 Supplement A): 443A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, coronary stenosis, heart disease, vascular disease, myocardial blood flow, vasodilator stress.

Haushalter, T.M., G.S. Friedrichs, D.L. Reynolds, M. Barecki Roach, G. Pastino, R. Hayes, and A.S. Bass (2008). **The cardiovascular and pharmacokinetic profile of dofetilide in conscious telemetered beagle dogs and cynomolgus monkeys.** *British Journal of Pharmacology* 154(7): 1457-64. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: BACKGROUND AND PURPOSE: The effects of dofetilide were studied in monkeys and dogs. Pharmacokinetic data were generated together with the monitoring of cardiovascular changes in order to compare effects relative to human exposure. EXPERIMENTAL APPROACH: Beagle dogs and cynomolgus monkeys were telemetered to collect arterial blood pressure, heart rate and ECG for 6 h after selected oral doses of dofetilide. Pharmacokinetic parameters were determined for each dose. KEY RESULTS: Dogs: increases in the QT(c) interval reached 56 ms in dogs dosed with 0.3 mg kg(-1) of dofetilide. Premature ventricular contractions and right bundle branch block were evident at this dose, without changes in cardiovascular parameters. The mean C(max) values were 3.35 and 60.15 ng mL(-1) at doses of 0.03 and 0.3 mg kg(-1), respectively. Monkeys: increases in QT(c) intervals reached 40-50 ms after 0.03 mg kg(-1). T-wave changes were observed after 0.03 mg kg(-1) without changes in cardiovascular parameters. The mean C(max) values following oral doses of 0.01 and 0.03 mg kg(-1) were 0.919 ng mL(-1) and 1.85 ng mL(-1), respectively. CONCLUSIONS AND IMPLICATIONS: Despite dofetilide exposure comparable to that in humans, QT(c) responses in dogs were greater than those reported in humans. A comparable human dose used in the monkey achieved only half of the exposure but was associated with twofold greater increases in QT(c). Our data support the view that safety risk assessments of new drugs in animal models should ensure that the clinical therapeutic range of exposure is achieved and any untoward effects interpreted accordingly.
Descriptors: anti arrhythmia agents toxicity, long qt syndrome chemically induced, models, animal, phenethylamines toxicity, sulfonamides toxicity, administration, oral, anti arrhythmia agents administration and dosage, anti arrhythmia agents pharmacokinetics, blood pressure

drug effects, dogs, dose response relationship, drug, electrocardiography, heart rate drug effects, macaca fascicularis, phenethylamines administration and dosage, phenethylamines pharmacokinetics, species specificity, sulfonamides administration and dosage, sulfonamides pharmacokinetics, telemetry.

He, K.L., M. Dickstein, H.N. Sabbah, G.H. Yi, A. Gu, M. Maurer, C.M. Wei, J. Wang, and D. Burkhoff (2004). **Mechanisms of heart failure with well preserved ejection fraction in dogs following limited coronary microembolization**. *Cardiovascular Research* 64(1): 72-83. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Descriptors: animal model, induced myocardial injury, hemodynamics, microembolization, neurohormonal activation, cardiovascular system, heart failure, heart disease, etiology, coronary microembolization, diastolic dysfunction, ejection fraction, neurohormonal activation.

He, K.L., W. Hadad, G.H. Yi, H. Zhou, S. Mohri, J. Wang, and D. Burkhoff (2003). **Nonexcitatory electric signals improve systemic hemodynamics and cardiac contractility in conscious dogs with chronic heart failure.** *Journal of the American College of Cardiology* 41(6 Supplement A): 89A ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, chronic heart failure, heart disease, left ventricular function, chronic heart failure effects, nonexcitatory electric signal induced improvement, systemic hemodynamics.

He, K.L., W. Sherman, G.H. Yi, Q. Li, H. Zhou, E.M. Becker, A.G. Gu, J. Harvey, E. Rose, H.B. Haimes, R. Kao, G.P. Zhang, M.J. Lee, J. Wang, and D. Burkhoff (2003). **Autologous skeletal myoblast transplantation improves hemodynamics and left ventricular regional and global function in conscious dogs with chronic heart failure.** *Cell Transplantation* 12(2): 146. ISSN: 0963-6897.
NAL Call Number: RM287.C45
Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, surgery, medical sciences, veterinary medicine, chronic heart failure, heart disease, autologous skeletal myoblast transplantation, laboratory techniques, echocardiography, clinical techniques, diagnostic techniques, inferior vena cava occlusion, experimental surgical techniques, skeletal muscle biopsy, ejection fraction, hemodynamics, mean aortic pressure, regional segment length, determination.

Hobai, I.A., C. Maack, and B. O'rourke (2004). **Partial inhibition of sodium/calcium exchange restores cellular calcium handling in canine heart failure**. *Circulation Research* 95(3): 292-299. ISSN: 0009-7330.
NAL Call Number: RC681.A1A57137
Abstract: Sodium/calcium (Na+/Ca2+) exchange (NCX) overexpression is common to human heart failure and heart failure in many animal models, but its specific contribution to the cellular Ca2+ ((Ca2+)i) handling deficit is unclear. Here, we investigate the effects of exchange inhibitory peptide (XIP) on Ca2+ handling in myocytes isolated from canine tachycardic pacing-induced failing hearts. Whole-cell patch-clamped left ventricular myo-

cytes from failing hearts (F) showed a 52% decrease in steady-state sarcoplasmic reticulum (SR) Ca2+ load and a 44% reduction in the amplitude of the (Ca2+)i transient, as compared with myocytes from normal hearts (N). Intracellular application of XIP (30 mumol/L) normalized the (Ca2+)i transient amplitude in F (3.86-fold increase), concomitant with a similar increase in SR Ca2+ load. The degree of NCX inhibition at this concentration of XIP was apprxeq27% and was selective for NCX: L-type Ca2+ currents and plasmalemmal Ca2+ pumps were not affected. XIP also indirectly improved the rate of (Ca2+)i removal at steady-state, secondary to Ca2+-dependent activation of SR Ca2+ uptake. The findings indicate that in the failing heart cell, NCX inhibition can improve SR Ca2+ load by shifting the balance of Ca2+ fluxes away from trans-sarcolemmal efflux toward SR accumulation. Hence, inhibition of the Ca2+ efflux mode of the exchanger could potentially be an effective therapeutic strategy for improving contractility in congestive heart failure.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, veterinary medicine, medical sciences, congestive heart failure.

Ishizaka, T., A. Takahara, H. Iwasaki, Y. Mitsumori, H. Kise, Y. Nakamura, and A. Sugiyama (2008). **Comparison of electropharmacological effects of bepridil and sotalol in halothane-anesthetized dogs.** *Circulation Journal Official Journal of the Japanese Circulation Society* 72(6): 1003-11. ISSN: 1346-9843.
Abstract: BACKGROUND: Bepridil is known to have a multiple ion channel-blocking property in the heart, which has been applied for the treatment of atrial fibrillation and drug-refractory ventricular tachyarrhythmias. In this study, the electro-pharmacological effects of bepridil were compared with those of dl-sotalol, a representative class III antiarrhythmic drug, using the halothane-anesthetized canine model. METHODS AND RESULTS: Cardiovascular and electrophysiological variables were measured under the halothane anesthesia. Intravenous administration of bepridil (0.3 mg/kg, n=4) delayed the intraventricular conduction and prolonged the ventricular effective refractory period, whereas dl-sotalol (0.3 mg/kg, iv, n=4) inhibited atrioventricular conduction and prolonged the atrial and ventricular effective refractory period. The additional administration of 10 times the higher dose of bepridil or dl-sotalol (ie, 3 mg/kg, iv, n=4 for each group) decreased blood pressure, suppressed ventricular contraction and sinus automaticity, and prolonged the atrial and ventricular effective refractory period and monophasic action potential duration, in addition to the effects of the low dose. CONCLUSIONS: The electropharmacological effects of bepridil and dl-sotalol were similar, although their potency for each cardiovascular variable varied significantly. These findings can be useful when selecting these drugs according to the pathophysiological condition of a patient.
Descriptors: adrenergic beta antagonists pharmacology, bepridil pharmacology, heart conduction system drug effects, sotalol pharmacology, vasodilator agents pharmacology, adrenergic beta antagonists blood, anesthetics, inhalation, atrioventricular node drug effects, bepridil blood, bundle of his drug effects, dogs, dose response relationship, drug, electrocardiography drug effects, halothane, models, animal, myocardial contraction drug effects, pacemaker, artificial, sinoatrial node drug effects, sotalol blood, vasodilator agents blood.

Ito, B.R., J. Ryan, S.C. Potter, and M.A. Young (1995). **Contractile dysfunction with arbutamine stress correlates with heart rate in conscious dog with coronary stenosis**. *Circulation* 92(8 SUPPL.): I479. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, coronary artery disease, diagnostic method, meeting abstract

Kador, P.F., K. Blessing, and M. Wyman (2003). **The results of combretastatin in galactose - fed dogs with diabetes - like proliferative retinopathy**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*
Abstract: Purpose: Combretastatin A-4 (CA4P) is a vascular targeting agent that has been reported to be capable of destroying newly formed capillary endothelial cells in growing vessels. The net effect of this drug has been to rapidly shut off blood flow in newly growing vessels and, as a result, regress neovascularization. The purpose of this study was to determine whether retinal neovascularization which results in altered retinal vessel blood flow and retinal permeability in the long-term galactose-fed dog can be halted with CA4P. Methods: All experiments conform to the ARVO Resolution on the Use of Animals in Research and NIH ACUC Guidelines. Eight beagles fed 30% galactose diet for 80-104 months and four age-matched control dogs were surgically made aphakic. Following recovery the dogs were divided into two groups each containing 4 galactose-fed dogs and 2 age-matched controls dogs with each group receiving CA4P either as sub-Tenon's injections administered at the corneoscleral junction or intravitreal injections. Six weeks after initial CA4P treatment all dogs also received systemic (IV) injections of CA4P. The extent of neovascularization and affect of CA4P administration were monitored by fluorescein angiography and color and monochromatic fundus photography at 2-week intervals. Results: Although CA4P was well tolerated by the healthy eyes of the control animals its administration to galactose-fed dogs was associated with corneal edema and increases in IOP after sub-Tenon's and intraocular injections. All galactose-fed dogs demonstrated retinal neovascular lesions and these were not ameliorated by either sub-Tenon's, intravitreal or systemic CA4P administration. Conclusions: Neovascularization in this animal model progresses over a period of years similar to that observed clinically. The failure of CA4P to ameliorate neovascularization suggests that chronic, long-term administration is required to destroy the slowly growing retinal endothelial cells.
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, sense organs, sensory reception, aphakia, eye disease, diabetes like proliferative retinopathy, endocrine disease, pancreas, metabolic disease, retinal blood vessel blood flow, retinal neovascularization.

Karapinar, K., A.T. Ulus, U. Tutun, A. Aksoyek, N. Apaydin, K. Pamuk, Z. Can, Z. Saritas, F. Kucukay, K. Arda, and S.F. Katircioglu (2004). **Implantation of novel small-diameter polyurethane vascular prostheses interposed in canine femoral and carotid arteries**. *European Surgical Research* 36(4): 241-248. ISSN: 0014-312X.
Descriptors: bioprocess engineering, cardiovascular system, transport and circulation, scanning electron microscopy, imaging and microscopy techniques, laboratory techniques,

vascular grafts, small diameter polyurethane vascular prosthesis, carotid artery interposition, femoral artery interposition.

Kassotis, J., R.B. Sauberman, C. Cabo, A.L. Wit, and J. Coromilas (2003). **Beta receptor blockade potentiates the antiarrhythmic actions of d-sotalol on reentrant ventricular tachycardia in a canine model of myocardial infarction.** *Journal of Cardiovascular Electrophysiology* 14(11): 1233-1244. ISSN: 1045-3873.

Abstract: Introduction: The importance of beta receptor blockade for the antiarrhythmic action of sotalol has not been completely elucidated. We determined how beta receptor blockade interacts with the effects of potassium channel blockade on reentrant circuits. Methods and Results: Sustained ventricular tachycardia was induced by programmed stimulation in dogs 4 days after left anterior coronary artery occlusion and reentrant circuits in the epicardial border zone (EBZ) mapped. The effects of the beta receptor-blocking drug, esmolol, the potassium channel-blocking drug d-sotalol, which lacks beta receptor-blocking effects, and the combination of the two drugs on the reentrant circuits that cause tachycardia were determined. Esmolol did not alter the ability to induce tachycardia. Small changes in the location or extent of lines of block in reentrant circuits accounted for small decreases or increases in tachycardia cycle lengths. d-Sotalol prolonged the lines of block in reentrant circuits, slowed propagation around the circuits, and prolonged tachycardia cycle length, but it did not stop tachycardia or prevent the induction of tachycardia. The combination of esmolol and d-sotalol prevented the initiation of sustained tachycardia. The stimulated premature impulse either blocked before reentering or traversed the circuit several times prior to blocking in a region of fractionated electrograms. The addition of esmolol to d-sotalol abolished the reverse use-dependent effects of d-sotalol alone on effective refractory period (ERP) and significantly prolonged ERP in the area of the reentrant circuit. Conclusion: Beta receptor blockade is important for the antiarrhythmic effects of d,l-sotalol on reentrant ventricular tachycardia in this model. The mechanism is speculative but may involve potentiation of d-sotalol actions to prolong ERP or effects on gap junctions.

Descriptors: cardiovascular system, transport and circulation, coronary artery occlusion, heart disease, reentrant ventricular tachycardia, effective refractory period.

Kast, R., H. Schirok, S. Figueroa Perez, J. Mittendorf, M.J. Gnoth, H. Apeler, J. Lenz, J.K. Franz, A. Knorr, J. Hutter, M. Lobell, K. Zimmermann, K. Munter, K.H. Augstein, H. Ehmke, and J.P. Stasch (2007). **Cardiovascular effects of a novel potent and highly selective azaindole-based inhibitor of Rho-kinase.** *British Journal of Pharmacology* 152(7): 1070-80. ISSN: 0007-1188.

NAL Call Number: 396.8 B77

Abstract: BACKGROUND AND PURPOSE: Rho-kinase (ROCK) has been implicated in the pathophysiology of altered vasoregulation leading to hypertension. Here we describe the pharmacological characterization of a potent, highly selective and orally active ROCK inhibitor, the derivative of a class of azaindoles, azaindole 1 (6-chloro-N4-{3,5-difluoro-4-[(3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]-phenyl}pyrimidine-2,4-diamine). EXPERIMENTAL APPROACH: Pharmacological characterization of azaindole 1 was performed with human recombinant ROCK in vitro. Vasodilator activity was determined using isolated vessels in vitro and different animal models in vivo. KEY RESULTS: This compound

inhibited the ROCK-1 and ROCK-2 isoenzymes with IC50 s of 0.6 and 1.1 nM in an ATP-competitive manner. Although ATP-competitive, azaindole 1 was inactive against 89 kinases (IC50>10 microM) and showed only weak activity against an additional 21 different kinases (IC50=1-10 microM). Only the kinases TRK und FLT3 were inhibited by azaindole 1 in the sub-micromolar range, albeit with IC50 values of 252 and 303 nM, respectively. In vivo, azaindole 1 lowered blood pressure dose-dependently after i.v. administration in anaesthetized normotensive rats. In conscious normotensive and spontaneously hypertensive rats azaindole 1 induced a dose-dependent decrease in blood pressure after oral administration without inducing a significant reflex increase in heart rate. In anaesthetized dogs, azaindole 1 induced vasodilatation with a moderately elevated heart rate. CONCLUSIONS AND IMPLICATIONS: Azaindole 1 is representative of a new class of selective and potent ROCK inhibitors and is a valuable tool for the elucidation of the role of ROCK in the cardiovascular system.

Descriptors: cardiovascular system drug effects, diamines pharmacology, protein kinase inhibitors pharmacology, pyrimidines pharmacology, rho associated kinases antagonists and inhibitors, administration, oral, apoptosis regulatory proteins antagonists and inhibitors, apoptosis regulatory proteins genetics, apoptosis regulatory proteins metabolism, binding sites drug effects, blood pressure drug effects, calcium calmodulin dependent protein kinases antagonists and inhibitors, calcium calmodulin dependent protein kinases genetics, calcium calmodulin dependent protein kinases metabolism, cells, cultured, computer simulation, dogs, dose response relationship, drug, injections, intravenous, mice, models, animal, models, molecular, organ culture techniques, phosphorylation, polymerase chain reaction methods, protein kinase inhibitors administration and dosage, protein kinase inhibitors chemistry, rabbits, rats, rats, inbred shr, rats, wistar, recombinant proteins antagonists and inhibitors, recombinant proteins genetics, recombinant proteins metabolism, time factors, vasodilator agents administration and dosage, vasodilator agents chemistry, vasodilator agents pharmacology, rho associated kinases genetics, rho associated kinases metabolism.

Kawase, A., T. Ikeda, K. Nakazawa, T. Ashihara, T. Namba, T. Kubota, K. Sugi, and H. Hirai (2003). **Widening of the excitable gap and enlargement of the core of reentry during atrial fibrillation with a pure sodium channel blocker in canine atria.** *Circulation* 107(6): 905-910. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8

Abstract: Background: This study aimed to assess the effects of pilsicainide, a pure sodium channel blocker, on electrophysiological action and wavefront dynamics during atrial fibrillation (AF). Methods and Results: In a newly developed model of isolated, perfused, and superfused canine atria (n=12), the right and left endocardia were mapped simultaneously by use of a computerized mapping system. AF was induced with 1 to 5 mumol/L acetylcholine. The antifibrillatory actions of pilsicainide on AF cycle length (AFCL), refractory period (RP), conduction velocity (CV), excitable gap (EG), and the core of the mother rotor were studied. The RP was defined as the shortest coupling interval that could capture the fibrillating atrium. The EG was estimated as the difference between the AFCL and RP. At baseline, multiple wavefronts were observed. After 2.5 mug/mL infusion of pilsicainide, all preparations showed irregular activity, and AF was terminated in 2 preparations. The AFCL and RP were prolonged, and CV was decreased significantly. The EG was widened (147%; P<0.01), and

the core perimeter was increased (100%; P<0.01). Increasing the dosage either terminated AF (6 preparations) or converted to organized activity (ie, atypical atrial flutter) (4 preparations). On the maps, all "unorganized" AFs were terminated with the excitation of the core of the mother rotor by an outside wavefront, whereas in preparations with atrial flutter, pilsicainide did not terminate its activity. Conclusions: Widening of the EG by pilsicainide facilitates the excitation of the core of the mother rotor, leading to the termination of AF. In some experiments, pilsicainide converts AF to persistent atrial flutter.

Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial fibrillation, heart disease, drug therapy, pathology, electrophysiology, clinical techniques, conduction velocity, cycle length, excitable gap widening, reentry core enlargement, refractory period, wavefront dynamics.

Keenan, C.M. and J.D. Vidal (2006). **Standard morphologic evaluation of the heart in the laboratory dog and monkey.** *Toxicologic Pathology* 34(1): 67-74. ISSN: 0192-6233.

Abstract: The nonrodent species most commonly utilized in preclinical safety studies are the purpose-bred beagle dog and cynomolgus macaque (Macaca fascicularis). Potential effects of a new chemical entity (NCE) on the heart pose serious concerns; consequently in vivo testing is focused on detection of functional alterations as well as morphological changes. Macroscopic and microscopic evaluation of the heart is based on a standard survey of key structures to properly assess presence of spontaneous and potential drug-induced lesions. Evaluation of historical controls to determine type and frequency of background change is valuable, as studies with non-rodent species generally have a small sample size. Archived control dog and monkey data were retrospectively reviewed, including terminal body weight (BW), heart weight (HW), and archival glass slides of heart. Control dogs had minimal background changes that included myxomatous or cartilagenous change in the cardiac skeleton and a variable degree of vacuolation in Purkinje fibers. Control monkey hearts commonly contained inflammatory cell infiltrates, myocyte anisokaryosis, and handling artifacts, while myocyte degeneration, squamous plaques, pigment, and intimal plaques were occasionally observed. These findings highlight the utility of consistently recorded and readily accessible archived control data when attempting to discern background spontaneous changes and artifacts from test-article induced changes.

Descriptors: dogs anatomy and histology, heart anatomy and histology, macaca fascicularis anatomy and histology, specimen handling standards, toxicity tests standards, body weight, drug evaluation, preclinical, organ size, reference values, species specificity, specimen handling methods, toxicity tests methods.

Kelly, C.M., M. Miyamoto, and S.J. Gosselin (2003). **Validation for qt prolongation in conscious beagle dogs administered sotalol via the oral route.** *Toxicological Sciences* 72(S-1): 32 ISSN: 1096-6080.

NAL Call Number: RA1190.F8

Descriptors: cardiovascular system, transport and circulation, pharmacology, toxicology, DSI telemetry system, medical equipment, williams test, laboratory techniques, implanted telemetry transmitters, medical supplies, ECG waveform, qt prolongation, blood pressure, heart rate.

Kemming, G., J.B. Messick, W. Mueller, G. Enders, F. Meisner, S. Muenzing, H. Kisch Wedel, A. Schropp, C. Wojtczyk, K. Packert, K. Messmer, and E. Thein (2004). **Can we continue research in splenectomized dogs? Mycoplasma haemocanis: old problem - new insight**. *European Surgical Research* 36(4): 198-205. ISSN: 0014-312X.
Descriptors: cardiovascular system, transport and circulation, infection, Mycoplasma haemocanis infection, bacterial disease, diagnosis, therapy, blood smear, diagnostic techniques, laboratory techniques, specific polymerase chain reaction, genetic techniques.

Kerbaul, F., B. Rondelet, S. Motte, P. Fesler, I. Hubloue, P. Ewalenko, R. Naeije, and S. Brimioulle (2004). **Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure.** *Critical Care Medicine* 32(4): 1035-40. ISSN: 0090-3493.
Abstract: OBJECTIVE: A transient increase in pulmonary arterial (PA) pressure can persistently depress right ventricular (RV) contractility. We investigated the effects norepinephrine and dobutamine on RV-PA coupling in this model of RV failure. DESIGN: Prospective, controlled, randomized animal study. SETTING: University research laboratory. SUBJECTS: Twenty-two anesthetized dogs. INTERVENTIONS: Animals underwent transient (90-min) PA constriction to induce persistent RV failure. They were randomly assigned to control, norepinephrine, or dobutamine group. Norepinephrine was administered at 0.1 and 0.5 microg x kg x min or dobutamine at 5 and 10 microg x kg x min. MEASUREMENTS AND MAIN RESULTS: We measured PA distal resistance and proximal elastance by pressure-flow relationships and vascular impedance. We also measured RV contractility by the end-systolic pressure-volume relationship (Ees), PA effective elastance by the end-diastolic to end-systolic relationship (Ea), and RV-PA coupling efficiency by the Ees/Ea ratio. The transient PA constriction persistently increased PA resistance and elastance, increased Ea from 0.8+/-0.1 to 2.7+/-0.3 mmHg/mL, decreased Ees from 1.1+/-0.1 to 0.5+/-0.1 mm Hg/mL, and decreased Ees/Ea from 1.2+/-0.1 to 0.2+/-0.1. Norepinephrine restored arterial pressure, increased RV contractility, and increased but did not normalize RV-PA coupling and cardiac output. Dobutamine restored arterial pressure, markedly increased RV contractility, and normalized RV-PA coupling and cardiac output. Compared with norepinephrine, dobutamine decreased PA resistance and elastance and increased RV contractility and RV-PA coupling. CONCLUSIONS: A transient increase in PA pressure persistently worsens PA hemodynamics, RV contractility, RV-PA coupling, and cardiac output. Dobutamine restores RV-PA coupling and cardiac output better than norepinephrine because of its more pronounced inotropic effect.
Descriptors: animal model, pulmonary arterial (PA) pressure, right ventricular (RV) contractility, cardiac output, norepinephrine, dobutamine.

Kim, J.T., K.Y. Rhee, J.H. Bahk, S.H. Do, Y.J. Lim, H. Ko, and K.H. Lee (2003). **Continuous mixed venous oxygen saturation, not mean blood pressure, is associated with early bupivacaine cardiotoxicity in dogs.** *Canadian Journal of Anesthesia* 50(4): 376-381. ISSN: 0832-610X.
Abstract: Purpose: To investigate changes of continuous mixed venous oxygen saturation (cSvO2) and mean arterial blood pressure (MBP) in dogs with bupivacaine-induced cardiac depression. Methods: Bupivacaine was infused into pentobarbital-anesthetized mongrel dogs (n=8) at a rate of 0.5 mgcntdotkg-1cntdotmin-1 until the MBP was 40 mmHg or less (end of bupivacaine infusion; BIE). The infusion time was divided into the early period, first 30

min of bupivacaine infusion and the late period, which was from 30 min of bupivacaine infusion until BIE. cSvO2 was monitored using a fibreoptic pulmonary artery catheter, and MBP and cardiac output (CO) were measured every ten minutes after the initiation of bupivacaine infusion. Arterial blood gas, serum electrolyte and bupivacaine concentration were measured simultaneously. The relationships between CO and cSvO2, and of CO vs MBP were compared by regression analysis in the early and late periods. Results: The Pearson's correlation coefficients between CO and cSvO2 were 0.782 (P=2.1X10-7) in the early period and 0.824 (P=1.3X10-6) in the late period. The correlation coefficients between CO and MBP were 0.019 (P=0.921) in the early period and 0.799 (P=4.8X10-6) in the late period. Conclusions: cSvO2, but not MBP, is associated with CO changes in bupivacaine-induced cardiac depression during the early period of bupivacaine intoxication. Decrease of MBP with low cSvO2 observed during the late period might imply severe cardiac depression induced by bupivacaine infusion.
Descriptors: cardiovascular system, transport and circulation, pharmacology, toxicology, bupivacaine induced cardiac depression, heart disease, toxicity, continuous mixed venous oxygen saturation, bupivacaine induced cardiotoxicity association, mean blood pressure.

Kita, T., K. Kubo, I. Narushima, S. Matsumura, Y. Yonetani, and T. Nakashima (1996). **Behavioral effects and role of endothelin in a canine subarachnoid model**. *Japanese Journal of Pharmacology* 71(SUPPL. 1): 91P. ISSN: 0021-5198.
Descriptors: behavior, cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, animal model, basilar artery caliber, behavioral effect, cerebral vasospasm, endocrine system, endothelin 1, meeting poster, meningeal sign, nervous system disease, severe ataxia, subarachnoid hemorrhage, vascular disease.

Kobayashi, T., K. Ashikaga, M. Kimura, K.I. Furukawa, K. Seya, T. Osanai, K. Okumura, and S. Motomura (2004). **Rapid atrial pacing upregulates synthesis of asymmetrical dimethylarginine and expression of protein arginine n-methyltransferases in canine af model.** *Journal of Pharmacological Sciences* 94(Supplement 1): 107P. ISSN: 1347-8613.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, atrial fibrillation, heart disease, rt pcr, reverse transcriptase polymerase chain reaction, genetic techniques, laboratory techniques, rapid atrial pacing, clinical techniques, therapeutic and prophylactic techniques.

Koide, M., S. Nishizawa, M. Yamaguchi, Y. Nonaka, and H. Namba (2004). **Chronological changes of diameter, functional properties, and morphology of vasospastic artery in canine two-hemorrhage model.** *Journal of Pharmacological Sciences* 94(Supplement 1): 94P. ISSN: 1347-8613.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, models and simulations, computational biology, hemorrhage, vascular disease, chronological changes, two hemorrhage model.

Koike, N., I. Takeyoshi, S. Ohki, M. Tokumine, K. Matsumoto, and Y. Morishita (2004). **Effects of adding p38 mitogen-activated protein-kinase inhibitor to celsior solution in canine heart transplantation from non-heart-beating donors.** *Transplantation* 77(2): 286-292. ISSN: 0041-1337.

NAL Call Number: QP89.T73

Abstract: Background: The activation of p38 mitogen-activated protein kinase (MAPK) plays an important role in ischemia-reperfusion injury. This study evaluated the effects of p38 MAPK inhibition using FR167653, a novel p38 MAPK inhibitor, as an additive to Celsior solution in canine heart transplantation from non-heart-beating donors (NHBDs). Methods: Donor hearts were left in situ for 20 minutes after cardiac arrest, which was induced by rapid exsanguination. Twelve donor-recipient pairs of mongrel dogs were divided into two groups: the control and FR167653 (FR) groups (n=6 each). In both groups, the grafts were subjected to coronary flushing and immersed in Celsior solution for 4 hours with or without FR167653. Orthotopic heart transplantation was then performed. Cardiac output (CO), left ventricular pressure (LVP), and end-systolic maximal elastance (Emax) were measured 2 hours after weaning from cardiopulmonary bypass (CPB), and the hearts were then harvested for histopathologic study. The activation of p38 MAPK was evaluated in another 20 mongrel dogs. Results: In the FR group, CO, LVP recovery rate, and Emax were significantly ($P<0.05$) higher 2 hours after weaning from CPB, histopathologic damage was attenuated, and the activation of p38 MAPK was significantly ($P<0.05$) inhibited 10 minutes after reperfusion compared with the control group. Conclusions: The addition of FR167653 to Celsior solution improved heart-graft viability, probably by way of the inhibition of p38 MAPK activation, which may attenuate ischemia-reperfusion injury in heart transplantation from NHBDs.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, ischemia reperfusion injury, vascular disease, heart transplantation, experimental surgical techniques, laboratory techniques, celsior solution, non heart beating donor.

Kojima, J., S. Niwano, M. Moriguchi, K. Ikeda, K. Inuo, J. Saito, and T. Izumi (2003). **Effect of pilsicainide on atrial electrophysiologic properties in the canine rapid atrial stimulation model: a possible suppressive effect on atrial electrical remodeling.** *Circulation Journal* 67(4): 340-346. ISSN: 1346-9843.

Abstract: The heterogeneous process of atrial electrical remodeling (AER) in the canine rapid atrial stimulation model has been previously reported although it has been reported that a sodium channel blocker might suppress the shortening of the atrial effective refractory period (AERP), its effect on long-term electrical remodeling is unknown. In the present study, the effect of pilsicainide on AER was evaluated. The right atrial appendage (RAA) was paced at 400 beats/min for 2 weeks. In the RAA, Bachmann's bundle (BB), the right atrium near the inferior vena cava (IVC) and in the left atrium (LA), AERP, AERP dispersion (AERPd) and the inducibility of atrial fibrillation (AF) were evaluated at several time points of the pacing phase and the recovery phase (1 week). The same protocol was performed during the administration of pilsicainide (4.5 mg/kg per day) and the parameters were compared with the controls. In the control dogs, the AERP was significantly shortened by rapid pacing at all atrial sites studied and the AERP shortening (DELTAAERP) was larger at the RAA and LA sites ($p<0.03$). However, pilsicainide decreased these DELTAAERPs at all 4 atrial sites.

AERPd was increased during the pacing phase whereas it was decreased during the recovery phase in the control dogs. In contrast, this pacing-induced AERPd was attenuated by the administration of pilsicainide. The AF inducibility was highest at the LA site in both groups, and the inducibility was lower in the pilsicainide group than the control group at all atrial sites. During the rapid pacing phase, the ventricular heart rate was significantly lower in the pilsicainide group than the control because of intra-atrial conduction block. In a canine rapid right atrial stimulation model, pilsicainide suppressed the shortening of the AERP at all atrial sites, possibly through the improvement of the hemodynamics as well as the action of the Na-Ca exchanger.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, atrial fibrillation, heart disease, atrial stimulation model, laboratory techniques, atrial effective refractory period, atrial electrical remodeling, atrial electrophysiology, ventricular heart rate.

Krause, S.-M., F.-C. Clayton, and D.-L.-J. Williams (2004). **Myocardial protection with the non-selective endothelin receptor antagonist l-753,037 following acute coronary artery occlusion in the dog.** *Journal of Cardiovascular Pharmacology* 43(2): 214-221. ISSN: 0160-2446.

Abstract: Efficacy of a new, potent non-selective endothelin antagonist, L-753037, was examined in a model of canine coronary artery occlusion and reperfusion to assess whether blockade of both ETA and ETB receptors would enhance or reduce myocardial ischemic injury. Instrumented dogs were randomized to receive vehicle (n=9) or L-753037 (0.1 mug/kg/min, n=9) by intracoronary infusion 30 minutes before a 90-minute LCx coronary artery occlusion and through 4 hours of reperfusion. After 4 hours of reperfusion, plasma ET-1 levels rose significantly in both groups: 24+-3 fmol/ml in vehicle animals (P<0.01) versus 42+-5 fmol/ml with L-753037 (P<0.05). Treatment with L-753037 normalized total LCx flow and regional myocardial flow after 4 hours of reperfusion in all regions. LCx flow was reduced 16% from pre-occlusion baseline (P=0.45) with treatment compared with 35% with vehicle (P<0.01). Endocardial flow in the risk region returned to baseline values with L-753037 treatment but was reduced apprx50% in vehicle animals. L-753037 treatment was associated with a 38% reduction in infarct size (24.1+-3.9% AAR with L-753037 treatment versus 38.7+-3.1% with vehicle, P<0.01). Thus, a non-selective endothelin antagonist provides significant myocardial protection primarily by improving regional myocardial flow distribution following reperfusion and demonstrated no detrimental effects associated with blockade of the ETB receptor.

Descriptors: cardiovascular system, transport and circulation, pharmacology, acute coronary artery occlusion, vascular disease, myocardial ischemic injury, heart disease, injury, myocardial protection.

Krolikowski, J.G., W. Gu, J.P. Tessmer, P.S. Pagel, D.C. Warltier, and J.R. Kersten (2004). **Sildenafil enhances coronary collateral development in dogs with diabetes**. *FASEB Journal* 18(4-5): Abst. 437.7. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: nitric oxide, phosphodiesterase fraction V inhibitor sildenafil, pharmacology, cardiovascular system, transport and circulation, endocrine system, chemical coordination

and homeostasis, diabetes mellitus, endocrine disease, pancreas, metabolic disease, coronary collateral development.

Kucukhuseyin, C. (2003). **Cardiovascular effects of intravenous pentazocine and cyclazocine in conscious, curarized-conscious, and anesthetized dogs.** *Journal of Basic and Clinical Physiology and Pharmacology* 14(3): 235-255. ISSN: 0792-6855.

Abstract: The cardiovascular effects of intravenous pentazocine and cyclazocine in dogs were studied under conscious, curarized-conscious (paralyzed by gallamine), and anesthetized states. In the conscious state, blood pressure and heart rate were dose-dependently increased by pentazocine (1, 2, 3 mg/kg) and to a lesser extent by cyclazocine (0.3 mg/kg). In all subsequent experiments on dogs, the results were obtained using 3 mg/kg pentazocine and 0.3 mg/kg cyclazocine. Pentazocine accelerated breathing, peaking at about 10 min, whereas cyclazocine reduced breathing to a minimum in 1 min, followed by a gradual recovery thereafter. In the curarized-conscious state, the blood pressure response to pentazocine was biphasic, namely an initial decrease followed by an increase; chronotrophic activity was stimulated. Pretreatment with either ganglionic or alpha andrenergic blocking agents not only significantly antagonized the pressory responses to the drug but also potentiated the initial decreases in blood pressure and unmasked a bradycardic component, but these parameters were not altered by 0.3 mg/kg naxalone. In open-chest anesthetized dogs, blood pressure, heart rate, contractility, and mean peripheral vascular resistance were simultaneously decreased by both pentazocine and cyclazocine, initially accompanied by increases in aortic blood flow. During the later stages of drug action, only the blood pressure and contractility were increased above control levels (biphasic effect). A comparison of blood pressure and heart rate responses to pentazocine in dogs kept under differing experimental conditions revealed that conscious dogs were more sensitive than curarized conscious and anesthetized animals to pentazocine action. In isolated guinea pig atria, the effect of adrenaline (0.1, 0.3, or 1 mg/mL) on the spontaneous breathing rate was significantly augmented by 10 mg/mL pentazocine ($p<0.02$ for 0.3 g/mL; $p<0.01$ for 0.1 g/mL adrenaline). In dogs, however, adrenaline (1 mg/kg)-induced increases in heart contractility, aortic blood flow, and blood pressure remained almost unaltered in the presence of pentazocine. We concluded that the above mentioned cardiovascular responses to pentazocine and cyclazocine are a consequence of the sum of the two following opposing effects: (i) an indirect reflex activation of sympathetic neuromediation in the periphery, and (ii) a direct membrane effect on the heart leading to bradycardia and a depression in myocardial contractility.

Descriptors: cardiovascular system, transport and circulation, pharmacology, curarization, experimental surgical techniques, laboratory techniques, blood pressure, conscious state, heart rate.

Kumagai, K., H. Nakashima, N. Gondo, and K. Saku (2003). **Antiarrhythmic effects of jtv-519, a novel cardioprotective drug, on atrial fibrillation/flutter in a canine sterile pericarditis model.** *Journal of Cardiovascular Electrophysiology* 14(8): 880-884. ISSN: 1045-3873.

Abstract: Introduction: A new cardioprotective drug, JTV-519, blocks Na+ current and inwardly rectifying K+ current and inhibits Ca2+ current. However, its role in atrial electrophysiology is unknown. We investigated the antiarrhythmic effects of JTV-519 on atrial fibrillation/flutter in the canine sterile pericarditis model. Methods and Results: In nine dogs

with sterile pericarditis, 38 episodes of sustained (>30 sec) atrial fibrillation (8 dogs) and 24 episodes of sustained atrial flutter (7 dogs) were induced by rapid atrial pacing. When atrial fibrillation or atrial flutter was sustained >15 minutes, it was cardioverted and reinduced. The inducibility of atrial fibrillation/flutter, the atrial effective refractory period, and the intra-atrial conduction time were compared before and after the continuous infusion of JTV-519 (0.03 mg/kg/min). JTV-519 significantly decreased the mean number of sustained atrial fibrillation episodes (from 4.2+-2.9 to 0+-0, P<0.01). In contrast, atrial flutter was still inducible in 4 dogs after JTV-519 (from 2.7+-2.5 to 1.6+-2.1, P=NS). JTV-519 significantly prolonged effective refractory period (from 123+-18 to 143+-14 msec, from 127+-18 to 151+-12 msec, and from 132+-13 to 159+-9 msec at basic cycle lengths of 200, 300, and 400 msec, respectively, P<0.01), but it did not affect the intra-atrial conduction time (from 47+-11 msec to 48+-11 msec, P=NS). Conclusion: JTV-519 had significant protective effects on atrial fibrillation in the canine sterile pericarditis model, mainly by increasing effective refractory period, suggesting that it may have potential as a novel antiarrhythmic agent for atrial fibrillation.

Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial fibrillation, heart disease, drug therapy, atrial flutter, heart disease, drug therapy, sterile pericarditis, electrophysiology, clinical techniques, atrial effective refractory period, calcium ion current, intra atrial conduction time, inwardly rectifying potassium ion current, sodium ion current.

Kumagai, K., H. Nakashima, and K. Saku (2003). **The hmg-coa reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in the canine sterile pericarditis model.** *Journal of the American College of Cardiology* 41(6 Supplement A): 90A. ISSN: 0735-1097.

NAL Call Number: RC681.A1

Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial fibrillation, heart disease, therapy, sterile pericarditis.

Kuniyoshi, T., Y. Kakihana, S. Isowaki, Y. Kanmura, and M. Tamura (2002). **Evaluation of cytochrome oxidase signal obtained by near-infrared spectroscopy during cardiopulmonary bypass in a dog model.** *2002 Annual Meeting of the American Society of Anesthesiologists, Orlando, FL, USA; October 12-16, 2002,*

Abstract: Although the signal obtained for cytochrome oxidase (cyt. ox.) by near-infrared spectroscopy (NIRS) should be a useful indicator of intracellular hypoxia and impending cerebral injury, the change in the cyt. ox. signal represents a small component of the total change, and is therefore vulnerable to artifact. Accordingly, data interpretation, especially of the cyt. ox. value, remains controversial. We have developed a new approach to the measurement of the redox state of cyt. ox. in the brain involving the use of our new algorithm, which has already been employed in clinical medicine1. In this paper, we used two different NIRS devices to examine possible cross-talk between the cytochrome and hemoglobin (Hb) signals while a change was occurring in the hematocrit. Methods: After institution of cardiopulmonary bypass (CPB), an aerobic (100% O2)-to-anaerobic (100% N2) transition was induced using a membrane oxygenator in 12 dogs to produce a maximum change (full scale) in cerebral oxygenation. After stabilization for 10 min under 100% O2, animals received 200 mg/kg of sodium cyanide to uncouple cytochrome from Hb. The hematocrit was then decreased

from 35 to 5% by hemodilution. During the experiments, the Hb and cytochrome signals were measured and calculations performed using two types of NIRS instrument: (1) NIRO 300 device (Hamamatsu Photonics Co., Hamamatsu, Japan), (2) OM 110 device (using our recently developed algorithm) (Shimadzu Co., Kyoto, Japan). Results: In this study, the Hb concentration calculated by either NIRS device (NIRO 300 or OM 110) showed a strong positive correlation with hematocrit values during hemodilution (NIRO 300: R2 = 0.96, p < 0.0001; OM 110: R2 = 0.98, p < 0.0001). Although the hemodilution resulted in a linear decrease in the cyt. ox. signal measured by the NIRO 300 device (R2 = 0.90, p < 0.0001), there was no correlation between the hematocrit value and the cyt. ox. signal measured by OM 110. Furthermore, the change in the cyt. ox. signal measured by OM 110 during hemodilution (from 35 to 5% Ht) was only 4 % of full scale. Discussion: After administration of a saturating quantity of sodium cyanide, mitochondrial oxygen consumption should be completely inhibited and the cyt. ox. signal should be independent of both the cerebral oxygen saturation and Hb concentration. Our data showed that the cyt. ox. signal calculated using our recently developed algorithm (OM 110 device) was not much influenced by hematocrit, but it showed a positive correlation with pump flow and hypoxia. However, the NIRO 300 device was unable to separate the Hb and cytochrome oxidase components during an attenuation, leading to artifactual changes in the cytochrome signal. In conclusion, the cyt. ox. signal measured by NIRS is dependent on the algorithm employed. Therefore, provided an accurate algorithm is employed the cyt. ox. signal measured by NIRS should provide us with important information even under CPB.

Descriptors: cardiovascular system, transport and circulation, cerebral injury, injury, nervous system disease, cardiopulmonary bypass, clinical techniques, therapeutic and prophylactic techniques, near infrared spectroscopy, laboratory techniques, spectrum analysis techniques, intracellular hypoxia.

Laky, D., L. Parascan, and V. Candea (2008). **Myocardial stunning. Morphological studies in acute experimental ischemia and intraoperatory myocardial biopsies.** *Romanian Journal of Morphology and Embryology; Revue Roumaine De Morphologie Et Embryologie* 49(2): 153-8. ISSN: 1220-0522.

Abstract: Myocardial stunning represent a consequence of brief ischemia with reversible regional contractile dysfunction dependent persist from minute to days after reperfusion, despite the absence of irreversible damage and restoration of coronary blood flow. The evolution of these new ischemic entity were described by experimental acute ischemia and repeated intraoperatory myocardial biopsies effectuated near 200 patients with heart disease, excluding those with cardiac failure and atrial fibrillation. Using histological histoenzymological and particularly ultrastructural methods, only reversible mitochondrial and sarcoplasmatic reticulum lesions, slight glycogen granules depletions and sporadical dissociation of myofilaments by edema were seen. Major mechanism for the state was suggested: generation of oxygen derived free radicals with consequent oxidative stress and impaired calcium homeostasis. Rare morphological appearance on stunned myocardium was signaled in the references, our collective first made these studies in Romania.

Descriptors: intraoperative period, myocardial ischemia pathology, myocardial stunning pathology, myocardium pathology, acute disease, biopsy, dogs, middle aged, models, animal.

Lall, S.C., K.V. Foyil, S. Sakamoto, R.K. Voeller, J.P. Boineau, R.J.J. Damiano, and R.B. Schuessler (2008). **Pulmonary vein isolation and the Cox maze procedure only partially denervate the atrium.** *Journal of Thoracic and Cardiovascular Surgery* 135(4): 894-900.

Abstract: OBJECTIVES: The effects of ablation lines on myocardial innervation and response to autonomic stimuli are unclear. This study examined the effects of radiofrequency ablation on atrial autonomic innervation and compared pulmonary vein isolation and the biatrial Cox maze procedure. METHODS: In 12 acute canines right and left vagosympathetic trunks and right and left stellate ganglia were isolated. Each nerve was stimulated before bipolar ablation, after pulmonary vein isolation, and after the Cox maze procedure. Nadolol (n = 6) and atropine (n = 6) were administered to block sympathetic and parasympathetic responses, respectively. Changes in heart rate and atrioventricular interval were compared. Changes in QRST area relative to an isoelectric baseline (index of local innervation) were calculated. RESULTS: Sympathetic stimulation of each nerve and parasympathetic stimulation of the vagosympathetic trunks caused significant changes in heart rate and atrioventricular interval. After pulmonary vein isolation, the effect of 33% of the nerves on heart rate changes was eliminated. The Cox maze procedure eliminated right stellate sympathetic effects on heart rate. Fifty percent of the nerves caused heart rate changes after the Cox maze procedure. There was no significant effect of either lesion set on atrioventricular interval changes. Stimulation of 50% of nerves after pulmonary vein isolation produced local area changes significantly different from control area. After the Cox maze procedure, a different 50% of the nerves produced local changes different from those seen after pulmonary vein isolation. CONCLUSIONS: Surgical ablation procedures disrupted innervation, affecting heart rate but not atrioventricular interval. Autonomic innervation affecting the atria was changed by pulmonary vein isolation and additionally by the Cox maze procedure. Residual autonomic effects were present even after the complete Cox maze procedure.

Descriptors: atrial fibrillation surgery, cardiac surgical procedures methods, catheter ablation, heart atria innervation, pulmonary veins surgery, dogs, heart atria surgery, models, animal.

Laurent, G., G. Moe, X. Hu, B. Holub, H. Leong Poi, J. Trogadis, K. Connelly, D. Courtman, B.H. Strauss, and P. Dorian (2008). **Long chain n-3 polyunsaturated fatty acids reduce atrial vulnerability in a novel canine pacing model.** *Cardiovascular Research* 77(1): 89-97. ISSN: 0008-6363.

NAL Call Number: QM178.A

Abstract: AIM: Our objective was to assess the effect of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on atrial fibrillation (AF) vulnerability and atrial structure in a new model of atrial cardiomyopathy. METHODS AND RESULTS: Dogs were studied in three groups: seven control dogs (UNPACED) and 24 dogs undergoing simultaneous atrioventricular pacing (for 2 weeks) assigned to placebo treatment (SAVP-PLACEBO, n = 12 dogs) or oral n-3 PUFAs (1 g/day) treatment (SAVP-PUFA, n = 12 dogs). SAVP-PUFA dogs had less AF inducibility (percentage of burst attempts leading to AF episodes: 5.5 +/- 7.4 vs. 20.4 +/- 14.2, P < 0.001) and maintenance [median AF duration: 601 s (377-1216) vs. 1598 s (1195-2400), P < 0.05] than SAVP-PLACEBO dogs. SAVP-PUFA dogs had significantly less local slowing of conduction and conduction heterogeneity than SAVP-PLACEBO dogs. SAVP-PUFA dogs had a significantly smaller increase in atrial matrix metalloproteinase-9

activity and in collagen type I and III messenger RNA expression (in arbitrary units) than SAVP-PLACEBO dogs (0.62 +/- 0.51 vs. 10.80 +/- 5.61, respectively for collagen I, P < 0.05; 1.66 +/- 0.48 vs. 5.24 +/- 1.16, respectively, for collagen III, P < 0.05). CONCLUSION: n-3 PUFA supplementation can reduce AF vulnerability in a new canine pacing model of atrial cardiomyopathy. The mechanism may be related to attenuation of collagen turnover.

Descriptors: atrial fibrillation prevention and control, cardiac pacing, artificial adverse effects, fatty acids, omega 3 pharmacology, atrial natriuretic factor blood, dogs, echocardiography, heart physiopathology, matrix metalloproteinase 9 metabolism, models, animal, myocardium pathology, transforming growth factor beta1 genetics.

Laurita, K.R., R. Katra, B. Wible, X. Wan, and M.H. Koo (2003). **Transmural heterogeneity of calcium handling in canine.** *Circulation Research* 92(6): 668-675. ISSN: 0009-7330.

NAL Call Number: RC681.A1A57137

Abstract: Spatial heterogeneity of the action potential and its influence on arrhythmia vulnerability is known. However, heterogeneity of intracellular calcium handling and, in particular, its effect on the electrophysiological substrate is less clear. Using optical mapping techniques, calcium transients and action potentials were recorded simultaneously from ventricular sites across the transmural wall of the arterially perfused canine left ventricular wedge preparation during steady-state baseline pacing and rapid pacing. During baseline pacing, the decay of intracellular calcium to diastolic levels and calcium transient duration were slower (70%, P<0.005) and longer (20%, P<0.005), respectively, closer to the endocardial surface compared with the epicardial surface. Tissue samples isolated from the left ventricular wall demonstrate that sarcoplasmic reticulum Ca2+ ATPase (SERCA2a) expression was significantly less in the subendocardial and midmyocardial layers compared with the subepicardial layer. In contrast, no significant difference in the transmural expression of Na+-Ca2+ exchanger was observed. During rapid pacing, calcium transient altemans and increased levels of diastolic intracellular calcium were significantly greater (P<0.01) closer to the endocardium (101%+-62% and 41%+-15%, respectively) compared with the epicardium (12%+-7% and 12%+-14%, respectively). In conclusion, cells closer to the endocardium exhibit a slower decay of intracellular calcium compared with cells near the epicardium, which may be due in part to reduced expression of SERCA2a. As a possible consequence, calcium transient alternans and increased diastolic levels of intracellular calcium may occur preferentially closer to the endocardial surface.

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, arrhythmia, heart disease, electrophysiology, clinical techniques, optical mapping, laboratory techniques, rapid pacing, steady state baseline pacing, clinical techniques, action potential, calcium handling, transmural heterogeneity, calcium transients.

Leach, J.K., E. Patterson, and E.A. O'rear (2004). **Encapsulation of a plasminogen activator speeds reperfusion, lessens infarct and reduces blood loss in a canine model of coronary artery thrombosis**. *Thrombosis and Haemostasis* 91(6): 1213-1218. ISSN: 0340-6245.

Abstract: In the present study, a polymer-encapsulated plasminogen activator was investigated as an alternative to restore blood flow more effectively than free plasminogen activator. While current fibrinolytic agents have limited efficacy, attributable to delayed onset of sus-

tained reperfusion and bleeding complications, encapsulated plasminogen activators have shown promise in addressing these shortcomings. A polymer-encapsulated plasminogen activator could offer an effective formulation with a prolonged shelf-life. In this study, coronary artery thrombosis was produced in the anesthetized dog by the injection of thrombin + whole blood, and then one of five randomly selected formulations was administered intravenously: saline, blank microcapsules, free streptokinase (FREE SK), streptokinase and blank microcapsules (FREE SK + BLANK), or streptokinase entrapped in polymer microcapsules (MESK). MESK significantly accelerated the time to reperfusion compared to FREE SK or FREE SK + BLANK. Additionally, substantial reductions were observed in residual clot mass, infarct mass, reocclusion episodes, fibrinogen depletion and blood loss with MESK compared to FREE SK. The results of this study demonstrate that MESK accelerates thrombolysis and the restoration of blood flow compared to identical dosages of FREE SK while also reducing systemic fibrinogenolysis and blood loss. Microencapsulation may produce an improved dosage form for restoring arterial blood flow and reducing bleeding complications with thrombolytic therapy.
Descriptors: cardiovascular system, transport and circulation, pharmacology, coronary artery thrombosis, heart disease, vascular disease, therapy.

Leather, H.A., P. Segers, N. Berends, E. Vandermeersch, and P.F. Wouters (2002). **Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension.** *Critical Care Medicine.* 30(11): 2548-52. ISSN: 0090-3493.
Abstract: OBJECTIVE: Arginine vasopressin is a promising systemic vasopressor in settings such as vasodilatory shock and cardiopulmonary resuscitation. The evidence that arginine vasopressin may also have a pulmonary vasodilatory effect makes it an attractive drug for the treatment of circulatory shock secondary to right ventricular failure and pulmonary hypertension. In the present study, we evaluated the effects of arginine vasopressin on right ventricular function and ventriculovascular coupling in the setting of moderate acute pulmonary hypertension and compared these effects with those of phenylephrine. DESIGN: Prospective laboratory investigation using an established model of acute pulmonary hypertension. SETTING: University hospital laboratory. SUBJECTS: Seven adult beagle dogs weighing 8-14 kg. INTERVENTIONS: After acute instrumentation to measure right ventricular pressure and volume with the conductance technique and pulmonary artery flow and pressure with high-fidelity transducers, the stable thromboxane analogue U46619 was infused continuously to obtain stable pulmonary hypertension. Phenylephrine and arginine vasopressin were administered consecutively in continuous infusions at doses titrated to achieve a 25% increase in aortic pressure. MEASUREMENTS AND MAIN RESULTS: Phenylephrine and arginine vasopressin both increased total pulmonary vascular resistance and arterial elastance without influencing characteristic impedance. Both drugs decreased cardiac output and stroke volume. Right ventricular hydraulic power output was reduced by arginine vasopressin but not by phenylephrine. Most importantly, arginine vasopressin caused a 31% decrease in right ventricular contractility measured as the slope of the preload recruitable stroke work relationship, whereas contractility was preserved during phenylephrine infusion. CONCLUSIONS: In the present model, arginine vasopressin causes pulmonary vascular constriction and exerts an important negative inotropic effect on the right ventricle. These findings suggest that one should be cautious in the use of arginine vaso-

pressin when right ventricular function is compromised.
Descriptors: beagle dogs, adult, arginine vasopressin, pulmonary vascular resistance, pulmonary hypertension.

Lee, B.H., H.W. Seo, and S.E. Yoo (2004). **Cardioprotective effects of (2s,3r,4s)-n'-benzyl-n"-cyano-n-(3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2h-benzopyran-4-yl)-guanidine (kr-31372) in rats and dogs.** *Pharmacology* 70(2): 74-82. ISSN: 0031-7012.
NAL Call Number: RM1.P473
Abstract: The cardioprotective effects of (2S,3R,4S)-N'-benzyl-N"-cyano-N-(3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2H-benzopyran-4-yl)-guanidine (KR-31372) were evaluated against ischemic/reperfusion injury in isolated rat hearts in vitro and in anesthetized rats and dogs in vivo. In isolated perfused rat hearts subjected to a 30-min global ischemia/30-min reperfusion, KR-31372 (1-10 muM) significantly improved severe contracture (end-diastolic pressure and time to contracture), markedly reduced reperfusion lactate dehydrogenase release, and enhanced the recovery of reperfusion contractile function (left ventricular developed pressure and double product) in a concentration-dependent manner compared with the vehicle-treated group. In anesthetized rats subjected to a 45-min coronary occlusion and a 90-min reperfusion, intravenous KR-31372 dose-dependently reduced infarct size from 58.6% to 48.5, 48.1 and 39.6% at 0.3, 1.0 and 3.0 mg/kg, respectively ($p<0.05$). In anesthetized beagle dogs that underwent a 1.5-hour occlusion followed by a 5-hour reperfusion, KR-31372 (2 mg/kg, i.v.) markedly reduced infarct size from 57.0% in controls to 28.0% ($p<0.05$). The cardioprotective effects of KR-31372 on contractile function in globally ischemic rat hearts and on reperfusion injury in anesthetized rats were significantly reversed by pretreatment with selective adenosine triphosphate-sensitive potassium (KATP) channel blockers, sodium 5-hydroxydecanoate and glibenclamide. Taken together, these results indicate that KR-31372 possesses potent cardioprotective effects in rats and dogs and its effects may be mediated by activation of mitochondrial KATP channels.
Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemia, reperfusion injury, vascular disease, drug therapy, pathology, cardioprotection, double product, end diastolic pressure, left ventricular developed pressure, severe contracture.

Lee, C.H., J.M. Goo, K.T. Bae, H.J. Lee, K.G. Kim, E.J. Chun, C.M. Park, and J.G. Im (2007). **CTA contrast enhancement of the aorta and pulmonary artery: the effect of saline chase injected at two different rates in a canine experimental model.** *Investigative Radiology* 42(7): 486-90. ISSN: 0020-9996.
Abstract: OBJECTIVE: To investigate the effect of saline chase injected at 2 different rates on computed tomography (CT) angiography. MATERIALS AND METHODS: This study was approved by our institutional animal study committee. Three injection protocols were used; contrast injection (24 mL, 0.8 mL/s) without saline chase (protocol A), contrast injection with saline chase injected at the same rate as the contrast medium (protocol B), and contrast injection with saline chase injected at half the rate (0.4 mL/s) of the contrast medium (protocol C). In the 3 dogs used in our study, each of the protocols was applied twice for every dog resulting in a total of 18 sessions of monitoring scans. CT images were acquired every second at the fixed level of the aorta and pulmonary artery (PA). The duration

of plateau, plateau deviation, and peak arterial enhancement were computed and compared using the Kruskall-Wallis and Mann-Whitney U test. RESULTS: Peak contrast enhancements were significantly more delayed with protocol B than with protocol A in both the PA (B: 48 seconds, A: 30 seconds, P=0.024) and aorta (B: 46 seconds, A: 38 seconds, P=0.024). The duration of enhancement plateau was longer with protocol B than with protocol A in PA (B: 14.8 seconds, A: 9.0 seconds, P=0.002) and in aorta (B: 16.2 seconds, A: 11.6 seconds, P=0.004). Protocol C had the longest duration of plateau in both PA (34.5 seconds, P=0.002) and aorta (33.8 seconds, P=0.004) with uniform plateau enhancement. The peak enhancement values of protocol C, however, were substantially lower than that of protocol A and B in both the PA (A: 262 HU, B: 239 HU, C: 191 HU, P=0.001) and aorta (A: 263 HU, B: 268 HU, C: 210 HU, P=0.001). CONCLUSIONS: Saline chase prolongs the duration of plateau and delays peak enhancement of the pulmonary artery and aorta. Saline chase injected at half the rate of contrast medium injection allowed more uniform and prolonged plateau contrast enhancement than other protocols.
Descriptors: angiography instrumentation, aorta physiology, contrast media, pulmonary artery physiology, sodium chloride administration and dosage, tomography, x ray computed instrumentation, aorta pathology, dogs, models, animal, pulmonary artery pathology.

Lee, T.M., M.S. Lin, T.F. Chou, C.H. Tsai, and N.C. Chang (2004). **Adjunctive 17beta-estradiol administration reduces infarct size by altered expression of canine myocardial connexin43 protein**. *Cardiovascular Research* 63(1): 109-117. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Descriptors: cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, pharmacology, coronary occlusion, heart disease, ischemia, vascular disease, ischemia reperfusion injury, myocardial infarction, western blot, genetic techniques, confocal microscopy, imaging and microscopy techniques, lucigenin derived chemiluminescence, laboratory techniques, infarct size.

Letsou, G.V., E.M. Breznock, J. Whitehair, R.S. Kurtz, R. Jacobs, M.L. Leavitt, H. Sternberg, S. Shermer, S. Kehrer, J.M. Segall, M.A. Voelker, H.D. Waitz, and P.E. Segall (2003). **Resuscitating hypothermic dogs after 2 hours of circulatory arrest below 6degreec.** *Journal of Trauma Injury Infection and Critical Care* 54(5 Supplement): S177-S182. ISSN: 1079-6061.
Abstract: Background: Ultraprofound hypothermia may have a place in trauma rescue and resuscitation. We describe resuscitation of dogs after asanguineous perfusion and circulatory arrest of 2 hours at 2degree to 4degreeC. Methods: Nine dogs were cooled using a bypass apparatus and their circulating blood replaced with bicarbonated Hextend (Abbott, North Chicago, IL). Perfusion was continued to 2degree to 4degreeC, and 60 mL of 2 mol/L KCl and 20 mL of 50% MgSO4cntdot7H2O were infused intra-arterially, and circulation was arrested for 2 hours. The dogs were then rewarmed, transfused, defibrillated, weaned from by-pass, and allowed to awaken. Preoperative and postoperative biochemistry and hematology were compared. Results: Six dogs recovered fully. One of these dogs died of an infection 2 weeks later. Three other dogs never recovered because of technical or procedural difficulties. Biochemical and hematologic parameters were normal by 3 weeks. Conclusion: Hypothermic blood substitution with Hextend allows resuscitation after 2 hours of ice-cold circulatory arrest in dogs.

Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, methods and techniques, circulatory arrest, vascular disease, resuscitation, clinical techniques, therapeutic and prophylactic techniques, hypothermia.

Li Ying Qian , Yang Xiao Yan , Zhou Shun Chang , and Gong Pei Li (2003). **Effects of phenolic alkaloids of menispermum dauricum on the hemodynamics and coronary circulation in anesthetized dog.** *Yaoxue Xuebao* 38(9): 658-660. ISSN: 0513-4870.
Abstract: Aim: To observe the effect of phenolic alkaloids of Menispermum dauricum (PAMD) on the hemodynamics, coronary circulation and oxygen metabolism of the myocardium in anesthetized dogs. Methods: In this study, the changes of LVSP, LVEDP and +-dp/dtmax, the flow of coronary artery and myocardial energy metabolism were measured in anesthetized dog with PAMD or NS. Results: In the anesthetized dogs, compared with pretreatment status, PAMD at 3.5 and 7.0 mgcntdotkg-1 caused decreases in the left ventricular systolic pressure(LVSP), +-dp/dtmax, heart rate, the rate of oxygen utilization, the coronary and general peripheral resistance. It was found to increase myocardial oxygen and coronary flow. There were no significant change in the left ventricular end diastolic pressure (LVEDP). Conclusion: PAMD can ameliorate hemodynamics, coronary circulation and myocardial metabolism.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, coronary resistance, general peripheral resistance, heart rate, hemodynamics, left ventricular systolic pressure.
Language of Text: Chinese.

Ling, L.H., C.A. Moreno, T. Lombari, and C.P. Appleton (2003). **Flow propagation velocity is load dependent: evidence from an open-chest dog model.** *Circulation* 108(17 Supplement): IV-393. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, aortic occlusion, vascular disease, balloon aortic occlusion, experimental surgical techniques, laboratory techniques, echocardiography, clinical techniques, diagnostic techniques, right atrial pacing, clinical techniques, therapeutic and prophylactic techniques, lv diastolic dimension [left ventricular diastolic dimension], lv systolic dimension [left ventricular systolic dimension], cardiac output, ejection fraction wall stress, flow propagation velocity, load dependence, mean left atrial pressure, transmitral driving pressure

Liu, J.C., P.K. Kao, P. Chan, Y.H. Hsu, C.C. Hou, G.S. Lien, M.H. Hsieh, Y.J. Chen, and J.T. Cheng (2003). **Mechanism of the antihypertensive effect of stevioside in anesthetized dogs.** *Pharmacology* 67(1): 14-20. ISSN: 0031-7012.
NAL Call Number: RM1.P473
Abstract: Stevioside is a sweet-tasting glycoside isolated from the leaves of Stevia rebaudiana. It has been used as a noncaloric sugar substitute in Japan and Brazil for decades. Previous studies have shown that it lowered blood pressure in spontaneously hypertensive rats by intravenous injection. This study was designed to evaluate the hypotensive effect of stevioside in dogs and to define the underlying mechanism. After nasogastric administration of stevio-

side powder (200 mg/kg), the blood pressure of healthy mongrel dogs began to significantly decrease at 60 min and returned to baseline level at 180 min. The reduction of blood pressure was more rapid (at 5-10 min) and effective after intravenous injection. However, no significant change of blood pressure was noted after injection through left vertebral artery, implicating that the hypotensive effect is not related to the central nervous system. Stevioside also showed significant hypotensive effects in renal hypertensive dogs, in a dose-dependent manner. In cultured rat aortic smooth muscle cells (A7r5 cell line), stevioside can dose-dependently inhibit the stimulatory effects of vasopressin and phenylephrine on intracellular Ca2+ in a calcium-containing medium. However, no intracellular Ca2+ inhibitory effect was observed in calcium-free medium, implicating that stevioside may inhibit the Ca2+ influx from extracellular fluid. Our present data show that stevioside did not influence the calcium ionophore (A23187) induced Ca2+ influx, indicating that the antagonistic effect was through Ca2+ channels. This study confirmed that stevioside is an effective antihypertensive natural product, and its hypotensive mechanism may be probably due to inhibition of the Ca2+ influx.

Descriptors: cardiovascular system, transport and circulation, pharmacology, hypertension, vascular disease, drug therapy, hypotension, drug therapy, blood pressure, calcium ion influx.

Loh, P., S.Y. Ho, T. Kawara, R.N.W. Hauer, M.J. Janse, G. Breithardt, and J.M.T. De Bakker (2003). **Reentrant circuits in the canine atrioventricular node during atrial and ventricular echoes: electrophysiological and histological correlation.** *Circulation* 108(2): 231-238. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8

Abstract: Background: The anatomic-electrophysiological correlation of AV nodal reentry is unclear. To localize reentrant circuits during atrial and ventricular echoes and to characterize sites of slow conduction and block, we correlated histology with electrophysiology of the AV node. Methods and Results: In 10 isolated dog hearts, extracellular electrical activity was recorded in Koch's triangle at 208 or 247 sites (interelectrode distance, 0.5 and 0.3 mm) after removal of 0.7 to 1.5 mm of overlying atrial tissue. Resection did not affect refractory periods. Five hearts were subjected to histology. Complete atrial echoes were induced in 1 heart, incomplete atrial echoes in 5 hearts. Unidirectional conduction block occurred at the atrial-transitional cell junction in the superior area. Zones of slow conduction arose at the atrial-transitional or the transitional-compact node junction in the inferior area. Complete reentrant circuits of ventricular echoes were obtained in 5 hearts. Unidirectional conduction block occurred at the compact node-transitional cell junction in the superior area. Localized zones of slow conduction arose at the junctions between the different types of tissue in the inferior area. Conclusions: In the dog heart, tissue architecture and functional dissociation between the inferior and the superior region of the AV node enable dual physiology and reentry. Slow conduction and functional conduction block occur at the junctions between the different types of tissue in the AV nodal area. Atrial echoes were enabled by conduction block at the atrial-transitional cell junction, whereas during ventricular echoes conduction block occurred at the compact node-transitional cell junction.

Descriptors: cardiovascular medicine, human medicine, medical sciences, electrophysiology, clinical techniques, histology, histology and cytology techniques, laboratory techniques, atrial echo, atrial transitional cell junction, atrioventricular nodal reentry, anatomic electrophysi-

ological correlation, extracellular electrical activity, inferior area, mapping, slow conduction, block sites, superior area, transitional compact node junction, unidirectional conduction block, ventricular echo.

Lucats, L., L. Vinet, A. Bize, X. Monnet, D. Morin, J.B. Su, P. Rouet Benzineb, O. Cazorla, J.J. Mercadier, L. Hittinger, A. Berdeaux, and B. Ghaleh (2007). **The inotropic adaptation during late preconditioning against myocardial stunning is associated with an increase in FKBP12.6.** *Cardiovascular Research* 73(3): 560-7. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: The inotropic adaptation during late preconditioning against myocardial stunning is associated with an increase in FKBP12.6. by Laurence Lucats, Laurent Vinet, Alain Bize, Xavier Monnet, Didier Morin, Jin Bo Su, Patricia Rouet-Benzineb, Olivier Cazorla, Jean-Jacques Mercadier, Luc Hittinger, Alain Berdeaux, Bijan Ghaleh. OBJECTIVES: Late preconditioning reduces contractile dysfunction during myocardial stunning. Mechanisms involving adaptation of calcium handling during excitation-contraction coupling to late preconditioning remain to be established. Thus, we investigated whether the late preconditioned myocardium is associated with contractile adaptation and changes in the cardiac ryanodine receptor (RyR2) and its regulatory protein FKBP12.6. METHODS: Chronically instrumented conscious dogs (coronary occluder, ultrasonic crystals for sonomicrometry) underwent a 10-min coronary artery occlusion followed by reperfusion. They were studied 24 h later in the late preconditioned state (day 1). RESULTS: Maximal velocity of wall thickening at day 1 was increased as compared to corresponding baseline at day 0 (39+/-4 vs. 30+/-3 mm/s, $p < 0.05$) although systolic wall thickening was similar (2.8+/-0.2 vs. 2.9+/-0.2 mm), demonstrating a significant change in left ventricular inotropic state. Intracoronary infusion of ryanodine (0.5-6 microg) induced a dose-dependent decrease in wall thickening. In the late preconditioned state, this negative inotropic response was significantly reduced vs. control state, suggesting changes in sarcoplasmic reticulum (SR) Ca2+-release through RyR2. Immunoquantification of FKBP12.6 revealed a 2.8 fold ventricular increase after late preconditioning as compared to the control state. The amount of RyR2 and its phosphorylated state were similar and binding experiments did not reveal any alterations in B(max) or K(D) for RyR2. Calsequestrin, SERCA2a and phospholamban levels were not altered by late preconditioning. CONCLUSIONS: The late preconditioned myocardium is characterized by an adaptation of regional function associated with an increased expression of FKBP12.6. This demonstrates an adaptation of the SR Ca2+-release through RyR2 during late preconditioning.
Descriptors: ischemic preconditioning, myocardial, myocardial stunning metabolism, myocardium metabolism, tacrolimus binding proteins metabolism, binding sites, blotting, western methods, calcium metabolism, dogs, dose response relationship, drug, echocardiography, models, animal, myocardial contraction, myocardial reperfusion, myocardial stunning pathology, myocardial stunning physiopathology, myocardium pathology, protein binding, ryanodine pharmacology, ryanodine receptor calcium release channel analysis, ryanodine receptor calcium release channel metabolism, sarcoplasmic reticulum metabolism, tacrolimus binding proteins analysis, time factors.

Lynch, J.E., A. Pouch, R. Sanders, M. Hinders, K. Rudd, and J. Sevick (2007). **Gaseous microemboli sizing in extracorporeal circuits using ultrasound backscatter.** *Ultrasound in Medicine and Biology* 33(10): 1661-75. ISSN: 0301-5629.

NAL Call Number: QC244.U4

Abstract: This paper describes efforts to estimate the size of gaseous microemboli (GME) in extracorporeal blood circuits based on the amplitude of backscattered ultrasound, starting with analytic modeling of the scattering behavior of GME in blood. After neglecting resonance effects, this model predicts a linear relationship between the amplitude of backscattered echoes and the diameter of GME. Computer simulations based on the cylindrical acoustic finite integration technique were performed to test some of the simplifying assumptions of the analytical model, with the simulations predicting small deviations from the linear approximation that could be treated as random scatter. Ultrasonic and microscopic measurements of injected GME were then performed on a test circuit to determine the linear correlation coefficient between echo amplitude and GME diameter in conditions like those employed in real cardiopulmonary bypass (CPB) circuits. The correlation coefficient determined through this study was further validated in a closed-loop CPB circuit using canine blood. This study shows that the amplitude of ultrasonic backscattered echoes can be used to accurately estimate the size distribution of a population of detected GME when the spacing of emboli is great enough to minimize interference and other multi-path scattering effects. With the high flow rates found in CPB circuits, typically ranging from 2 to 6 L per minute (equivalent to a flow velocity of 0.3 to 1 m/s through the circuit tubing), this assumption will be valid even when hundreds of emboli per second pass through the circuit. Therefore, sizing of GME using the ultrasonic backscatter models described in this paper is a viable method for estimating embolic load delivered to a patient during a CPB procedure.

Descriptors: computer simulation, embolism, air ultrasonography, extracorporeal circulation adverse effects, image interpretation, computer assisted, algorithms, cardiopulmonary bypass adverse effects, dogs, models, animal, scattering, radiation, ultrasonics.

Maalej, N. and J.D. Folts (1996). **Effect of shear stress on acute thrombus formation in stenosed dog carotid arteries**. *FASEB Journal* 10(3): A565. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, nervous system, neural coordination, adhesion, aggregation, atherosclerosis, meeting abstract, myocardial infarction, platelet activation, stroke.

Mahmoudabady, M., M. Mathieu, L. Dewachter, I. Hadad, L. Ray, P. Jespers, S. Brimioulle, R. Naeije, and K. McEntee (2008). **Activin-A, transforming growth factor-beta, and myostatin signaling pathway in experimental dilated cardiomyopathy.** *Journal of Cardiac Failure* 14(8): 703-9.

NAL Call Number: RC685.C173

Abstract: BACKGROUND: The pathogenic mechanisms of dilated cardiomyopathy are still uncertain. A number of cytokines and growth factors participate in the remodeling process of the disease. METHODS: We investigated the cardiac myostatin, transforming growth factor (TGF)beta, and activin-A/Smad growth inhibitory signaling pathway in experimental dilated cardiomyopathy. Transvenous endomyocardial biopsies of the interventricular septum were

taken weekly in 15 beagle dogs during the development of heart failure (HF) induced by rapid pacing over a period of 7 weeks. Genes involved in the myostatin-TGFbeta-activin-A/Smad signaling pathway and the cardiac hypertrophic process were quantified by real-time quantitative polymerase chain reaction. Left ventricular volume, function, and mass were evaluated by echocardiography. RESULTS: Overpacing was associated with increased left ventricular volumes and decreased ejection fraction, whereas the left ventricular mass remained unchanged. TGFbeta was increased in moderate HF. Activin-A mRNA expression was 4-fold higher in overt congestive HF than at baseline. A 2-fold decrease of activin type II receptors and activin receptor interacting protein 2 gene expressions were observed, as well as a transient decrease of follistatin. Activin type I receptors, activin receptor interacting protein 1, follistatin-related gene, and myostatin remained unchanged. The inhibitory Smad 7, a negative feedback loop regulator of the Smad pathway, was overexpressed in severe HF. Gene expression of the cyclin-dependent kinase inhibitor p21, a direct target gene of the Smad pathway, was 8-fold up-regulated in HF, whereas cyclin D1 was down-regulated. CONCLUSION: We conclude that tachycardia-induced dilated cardiomyopathy is characterized by gene overexpression of the TGFbeta-activin-A/Smad signaling pathway and their target gene p21 and by the absence of ventricular hypertrophy.
Descriptors: activins metabolism, cardiomyopathy, dilated metabolism, cyclin d1 metabolism, cyclin dependent kinase inhibitor p21 metabolism, myostatin metabolism, signal transduction, cardiomyopathy, dilated genetics, cardiomyopathy, dilated ultrasonography, cytokines metabolism, disease progression, dogs, gene expression, intercellular signaling peptides and proteins metabolism, models, animal.

Mangrum, J.M., T.H.I. Everett, L.C. Kok, L. Shang, and D.E. Haines (1999). **Atrial mechanoelectric feedback in a chronic dog model: stretch dominates stress in atrial fibrillation vulnerability**. *Circulation* 100(18 SUPPL.): I.341. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, atrial fibrillation, heart disease, vulnerability, atrial mechanoelectric feedback, atrial stretch, atrial wall stress, meeting abstract.

Markos, F., B.A. Hennessy, M. Fitzpatrick, J. O'sullivan, and H.M. Snow (2002). **The effect of tezosentan, a non-selective endothelin receptor antagonist, on shear stress-induced changes in arterial diameter of the anaesthetized dog.** *Journal of Physiology* 544(3): 913-918. ISSN: 0022-3751.
NAL Call Number: 447.8 J82
Abstract: The effects of changes in the mean (Sm) and pulsatile (Sp) components of arterial wall shear stress on arterial dilatation of the iliac artery of the anaesthetized dog were examined in the absence and presence of the endothelin receptor antagonist tezosentan (10 mg kg-1 I.V.; Ro 61-0612; (5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide)). Changes in shear stress were brought about by varying local peripheral resistance and stroke volume using a distal infusion of acetylcholine and stimulation of the left ansa subclavia. An increase in Sm from 1.81+-0.3 to 7.29+-0.7 N m-2 (means+-S.E.M.) before tezosentan caused an endothelium-dependent arterial dilatation which was unaffected by administration

of tezosentan for a similar increase in Sm from 1.34+-0.6 to 5.76+-1.4 N m-2 (means+-S.E.M.). In contrast, increasing the Sp from 7.1+-0.8 to a maximum of 11.5+-1.1 N m-2 (means+-S.E.M.) before tezosentan reduced arterial diameter significantly. Importantly, after administration of tezosentan subsequent increases in Sp caused arterial dilatation for the same increase in Sp achieved prior to tezosentan, increasing from a baseline of 4.23+-0.4 to a maximum of 9.03+-0.9 N m-2 (means+-S.E.M.; P<0.001). In conclusion, the results of this study provide the first in vivo evidence that pulsatile shear stress is a stimulus for the release of endothelin from the vascular endothelium.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, arterial diameter, arterial dilatation, arterial wall shear stress, pulsatile components, endothelium dependent arterial dilatation, shear stress induced changes, stroke volume.

Markos, F., B.A. Hennessy, M. Fitzpatrick, J. O'sullivan, and H.M. Snow (2002). **Reverse arterial wall shear stress causes nitric oxide-dependent vasodilatation in the anaesthetised dog.** *Pfluegers Archiv European Journal of Physiology* 445(1): 51-54. ISSN: 0031-6768.
Abstract: The effects of a maintained increase in mean arterial wall shear stress (SSm) caused by blood flow in the normal and reverse direction on dilatation of the iliac artery were examined in the anaesthetised dog. Blood flow in the left iliac artery was varied in both the forwards and reverse directions by a perfusion pump connecting the right and left femoral arteries. An increase in blood flow, and therefore SSm in either direction, caused an increase in arterial diameter. However, an increase in forwards SSm (control 4.1+-0.11 mm) caused a significantly greater change in arterial diameter than an equivalent increase in the reverse direction (control 4.3+-0.08), 0.198+-0.02 mm vs. 0.132+-0.02 mm (mean+-SEM) respectively, for the same increase in SSm (3.23 N/m2). The increase in arterial diameter in response to an increase in forwards or reverse SSm was attenuated by L-NAME (80 mg/kg i.v.), indicating that the arterial dilatation was mediated by nitric oxide (NO). These findings confirm that endothelial NO release is dependent on the steady-state SSm and that the response occurs irrespective of the direction in which this force is applied, but is attenuated in the reverse direction.
Descriptors: cardiovascular system, transport and circulation, veterinary medicine, medical sciences, anesthesia, clinical techniques, shear stress, vasodilatation.

Masugata, H., B. Peters, S. Lafitte, B. Yao, M. Strachan, O.L. Kwan, K. Ohmori, K. Mizushige, and M. Kohno (2003). **Comparison of open- and closed-chest canine model for quantification of coronary stenosis severity by myocardial contrast echocardiography.** *Investigative Radiology* 38(1): 44-50. ISSN: 0020-9996.
Abstract: RATIONALE AND OBJECTIVES: The objective of the present study was to compare the data regarding the ability of real-time myocardial contrast echocardiography (MCE) to assess altered myocardial blood flow produced by graded coronary stenoses between open- and closed-chest canine models. MATERIALS AND METHODS: Three grades of left anterior descending coronary artery stenosis and occlusion were created in 6 open- and 6 closed-chest canine models. MCE used FS-069 infusion and real-time imaging. Myocardial signal intensity versus time plots were fitted to a 1-exponential function to obtain the peak signal intensity (A) and rate of signal intensity rise (b) for quantifica-

tion of myocardial blood flow. RESULTS: The value of b obtained from closed-chest canine models (without stenosis=0.995+-0.087, mild stenosis=0.968+-0.076, moderate stenosis=0.569+-0.077, severe stenosis=0.288+-0.032, occlusion=0.085+-0.031) was not significantly different from that obtained from open-chest canine models (without stenosis=1.028+-0.107, mild stenosis=0.998+-0.098, moderate stenosis=0.601+-0.055, severe stenosis=0.321+-0.029, occlusion=0.079+-0.028) at any grade of stenosis (P=0.09, 0.08, 0.44, 0.11, 0.74, respectively). CONCLUSIONS: In myocardial regions where attenuation of the ultrasound beam and artifacts produced by the chest wall are minimal, the data from transthoracic MCE in the closed-chest model may show values similar to those from MCE in the open-chest model.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, coronary stenosis, heart disease, vascular disease, diagnosis, closed chest model, laboratory techniques, myocardial contrast echocardiography, clinical techniques, diagnostic techniques, open chest model, laboratory techniques, peak signal intensity, signal intensity.

Mc Entee, K., C. Clercx, H. Amory, C. Michaux, J.J. Dardenne, D. Soyeur, and M. Henroteaux (1999). **Doppler echocardiographic study of left and right ventricular function during dobutamine stress testing in conscious healthy dogs**. *American Journal of Veterinary Research* 60(7): 865-871. ISSN: 0002-9645.

NAL Call Number: 41.8 Am3A

Abstract: Objective-To evaluate left and right ventricular filling and ejection performances by use of Doppler echocardiography in healthy, conscious dogs submitted to dobutamine stress testing. Animals-10 unsedated, healthy adult Beagles. Procedure-Doppler echocardiography was performed during cardiac stress testing on each dog twice at 24-hour intervals. Dobutamine was infused in 10 mug/kg of body weight/min incremental dosages, from 12.5 to 42.5 mug/kg/min. Duration of each step was 15 minutes. Doppler measurements were recorded at baseline and at each stage of dobutamine infusion, whereas aortic diameter was measured at baseline and at peak dosage by use of two-dimensional echocardiography. Results-Dobutamine infusion induced a significant increase in velocity time integrals and in peak flow velocities at the aortic, pulmonic, mitral, and tricuspid valves. Acceleration time-to-deceleration time ratio at the aortic wave also was increased significantly. On the other hand, ejection time, acceleration time, and deceleration time at the aortic and pulmonic valves and peak flow velocity of the E wave-to-peak flow velocity of the A wave ratio at the mitral and tricuspid valves decreased significantly during the test. The acceleration time-to-deceleration time ratio at the pulmonic wave was unchanged. A significant, progressive increase in cardiac index also was observed during dobutamine infusion, with a maximal increase of 104% from baseline. This was mediated initially by an increase in stroke index and, at higher dosages, by an increase in heart rate. Conclusions and Clinical Relevance-Doppler echocardiography performed during dobutamine stress testing may be a reliable method of assessing myocardial function in dogs with cardiovascular disease.

Descriptors: cardiovascular system, transport and circulation, radiology, medical sciences, veterinary medicine, medical sciences, dobutamine stress testing, evaluation method, doppler echocardiography, imaging method, myocardial function, assessment, left ventricular, right ventricular.

Mc Entee, K., C. Clercx, D. Soyeur, H. Amory, C. Michaux, T. Flandre, E. Jonville, C. Pynnaert, N. Miserque, and M. Henroteaux (2001). **Usefulness of dobutamine stress tests for detection of cardiac abnormalities in dogs with experimentally induced early left ventricular dysfunction**. *American Journal of Veterinary Research* 62(3): 448-455. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Abstract: Objective: To determine whether dobutamine stress tests (DST) can be used to detect cardiac dysfunction in dogs with early left ventricular dysfunction (ELVD) induced by rapid right ventricular pacing (RRVP). Animals: 7 adult male Beagles. Procedure: A pacemaker was surgically implanted in each dog at the level of the right ventricular apex. Electrocardiography, Doppler sphygmomanometry, and Doppler echocardiography were performed before and during a DST prior to activation of the pacemaker and every 3 to 4 days during the period of RRVP. Dobutamine stress tests were performed by infusing dobutamine at incremental dosages ranging from 12.5 to 42.5 mug/kg of body weight/min. Results: Clinical signs of congestive heart failure were not observed during the pacing period. However, all dogs developed ELVD associated with significant changes in values for most Doppler echocardiographic variables obtained prior to DST. Adverse cardiac effects were not detected during DST. Most Doppler echocardiographic indices of cardiac function were significantly altered in response to dobutamine infusion during the pacing period, compared with prepacing values. However, a dobutamine-induced 2-fold increase in cardiac output was maintained. Conclusions and Clinical Relevance: Dobutamine stress tests can be safely performed in dogs with experimentally induced ELVD. Dobutamine stress tests may be a sensitive, noninvasive diagnostic method, complementary to standard clinical examinations, for detection of early cardiac dysfunction in dogs asymptomatic for dilated cardiomyopathy.
Descriptors: veterinary medicine, medical sciences, methods and techniques, pharmacology, cardiovascular system, transport and circulation, cardiac abnormalities, heart disease, dilated cardiomyopathy, left ventricular dysfunction, experimentally induced early disease model, dobutamine stress test, detection method, diagnostic method.

Mehta, A., A.C. Jain, and M.C. Mehta (2003). **Electrocardiographic effects of intravenous cocaine: an experimental study in a canine model.** *Journal of Cardiovascular Pharmacology* 41(1): 25-30. ISSN: 0160-2446.
Abstract: Cocaine abuse causes cardiac dysfunction. Acute intravenous administration of cocaine may lead to development of severe arrhythmias, conduction abnormalities, ST-T changes, and sudden death. Understanding arrhythmogenesis due to cocaine may provide a therapeutic approach to reduce morbidity and mortality. We studied the arrhythmogenic activity and other electrocardiographic abnormalities resulting from an intravenous bolus of cocaine. Baseline and postanesthetic electrocardiographic findings were compared with those after administration of intravenous bolus of various doses of cocaine hydrochloride in 20 dogs. The study was done in three phases (phase I: low dose of cocaine (1 mg/kg, 15 experiments); phase II: medium dose (2 mg/kg, 30 experiments); and phase III: high dose (5-7 mg/kg, 10 experiments)). Plasma levels of cocaine were estimated. The low dose induced sinus bradycardia, sinus arrhythmia, atrial ectopic, wandering pacemaker, unifocal ventricular premature contractions, and ventricular couplets. The medium dose generated moderately severe arrhythmias that were of supraventricular origin. Atrial flutter and atrial fibrillation were observed in two experiments each. Ventricular arrhythmias were manifested as unifocal,

multifocal, interpolated ventricular premature contractions as well as bigeminy, trigeminy, couplets, and salvos. The high dose of 5-7 mg/kg increased electrocardiographic intervals and caused ST-segment elevation as well as serious life-threatening arrhythmias. Three of the dogs developed sustained ventricular tachycardia followed by ventricular flutter-fibrillation and death.
Descriptors: behavior, cardiovascular system, transport and circulation, toxicology, atrial ectopic, heart disease, atrial fibrillation, heart disease, atrial flutter, heart disease, cardiac arrhythmia, drug abuse, behavioral and mental disorders, sinus arrhythmia, sinus bradycardia, ventricular tachycardia, st changes, unifocal ventricular premature contractions, ventricular couplets, wandering pacemaker.

Miao, C.H., H. Jiang, and B. Sun (1997). **Inhaled nitric oxide improves ventilation efficiency and hemodynamic properties in dogs with endotoxin induced acute respiratory distress syndrome**. *Pediatric Research* 41(4 PART 2): 36A ISSN: 0031-3998.
NAL Call Number: RJ1.P4
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, toxicology, cardiovascular drug, critical care, endotoxin induced acute respiratory distress syndrome, gas exchange, hemodynamic properties, inhaled administration efficacy, nitric oxide, pharmacodynamics, pharmacokinetics, pharmacology, respiratory system, respiratory system disease, ventilation efficiency.

Milei J , Beigelman R , Valero E , Pesce R , Quel E , Armentano R , and Storino R (1990). **Histological features of the canine myocardium surrounding the laser beam crater**. *Archivos Del Instituto De Cardiologia De Mexico* 60(1): 21-26. ISSN: 0020-3785.
Abstract: Laser beam constitutes a potential therapy in modern cardiology. Although its myocardial effects are known, they have been insufficiently evaluated at the surviving myocytes zone surrounding the evaporated crater. In order to assess myocyte cellular and organellar damage, we studied 8 isolated canine hearts radiated with different intensities by a CO2He laser beam 2.4, 3.5, 5, 15, 25, 30 and 40 Watts, varying the exposition time from 1 to 6 sec. Color photographs from the post-radiated lesions on front and depth were obtained. Their volumes were measured applying the cylinder and the cut out-conus formulas according to the shape of the lesions and then the involved tissues were embedded in paraffin for histological studies. Previously, samples of the lesions were fixed in glutaraldehyde for ultrastructural studies. Volumes of the craters wre from 0.0004 to 19.57 mm3. Three layers were observed: (a) a carbonized internallining which measured x 15 microns in thickness; (b) a coagulation necrotic zone ("gruyere cheese-like"), 70 microns thickness; (c) finally more peripherally, a layer consisting of myocytes with patchy homogeneous cytoplasm, and scarse positivity for the Barbeito Lopex Trichome Stain (a positive technique in cases of myocardial damage). Ultrastructurally, crater peripheral cells showed cytosol and mitochondrial edema without membrane disruptions. These findings suggest that myocytes surrounding the laser beam crater, show reversible lesions. Therefore laser beam appears a safe procedure to be used in myocardium.
Descriptors: cardiovascular system, transport and circulation, cell biology, pathology, radiation biology, organelle damage myocyte cellular assessment laser therapy effects safe pro-

cedure.
Language of Text: Spanish.

Monaco, B.A., A. Benicio, I.S. Contreras, L.E. Mingrone, G. Ballester, and L.F. Moreira (2007). **Ischemic preconditioning and spinal cord function monitoring in the descending thoracic aorta approach.** *Arquivos Brasileiros De Cardiologia* 88(3): 291-6.
NAL Call Number: RC681.A1
Abstract: OBJECTIVES: To evaluate the effectiveness of acute ischemic preconditioning (IP), based on somatosensory evoked potentials (SSEP) monitoring, as a method of spinal cord protection and to asses SSEP importance in spinal cord neuromonitoring. METHODS: Twenty-eight dogs were submitted to spinal cord ischemic injury attained by descending thoracic aorta cross-clamping. In the C45 group, the aortic cross-clamping time was 45 min (n=7); in the IP45 group, the dogs were submitted to IP before the aortic cross-clamping for 45 min (n=7). In the C60 group, the dogs were submitted to 60 min of aortic cross-clamping (n=7), as in the IP60 group that was previously submitted to IP. The IP cycles were determined based on SSEP changes. RESULTS: Tarlov scores of the IP groups were significantly better than those of the controls (p = 0.005). Paraplegia was observed in 3 dogs from C45 and in 6 from C60 group, although all dogs from IP45 group were neurologically normal, as 4 dogs from IP60. There was a significant correlation between SSEP recovery time until one hour of aortic reperfusion and the neurological status (p = 0.011), showing sensitivity of 75% and specificity of 83%. CONCLUSION: Repetitive acute IP based on SSEP is a protection factor during spinal cord ischemia, decreasing paraplegia incidence. SSEP monitoring seems to be a good neurological injury assessment method during surgical procedures that involve spinal cord ischemia.
Descriptors: aorta, thoracic surgery, evoked potentials, somatosensory physiology, ischemic preconditioning standards, spinal cord ischemia diagnosis, spinal cord ischemia prevention and control, analysis of variance, dogs, ischemic preconditioning methods, models, animal, monitoring, intraoperative methods, paraplegia etiology, reperfusion methods, sensitivity and specificity, spinal cord blood supply, spinal cord physiopathology, spinal cord ischemia etiology, spinal cord ischemia physiopathology, statistics, nonparametric, time factors, vascular surgical procedures adverse effects.
Language of Text: Portuguese.

Monahan, T.S., N.D. Andersen, H. Panossian, J.A. Kalish, S. Daniel, G.V. Shrikhande, C. Ferran, and F.W. Logerfo (2007). **A novel function for cadherin 11/osteoblast-cadherin in vascular smooth muscle cells: modulation of cell migration and proliferation.** *Journal of Vascular Surgery Official Publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter* 45(3): 581-9. ISSN: 0741-5214.
Abstract: OBJECTIVE: Intimal hyperplasia is a common cause of vein graft failure in cardiovascular surgery. The molecular basis for intimal hyperplasia remains poorly defined. We have previously identified, by gene chip analysis of vein grafts, increased messenger (mRNA) for the adhesion molecule cadherin 11/osteoblast-cadherin (CDH11). The function of CDH11 in vascular cells is unknown. The aim of the present study is to confirm CDH11 expression in vein grafts and characterize its role in vascular remodeling. METHODS: Cephalic vein interposition grafts were implanted in a canine model and harvested at

predetermined time points. CDH11 protein expression was determined by immunohistochemistry. Early passage human coronary artery smooth muscle cells (SMCs) were used for in vitro studies. Real-time polymerase chain reaction was used to assess cellular CDH11 mRNA levels. CDH11 signaling was inhibited by either transfection with silencing RNA targeting CDH11 or with a blocking antibody to CDH11. Cellular migration was evaluated and cellular proliferation was assessed. RESULTS: Expression of CDH11 was increased in medial SMCs of vein grafts recovered at 7, 14, and 30 days after surgery compared with control veins from the same animals. In vitro CDH11 mRNA was up-regulated 1.8 +/- 0.2-fold (P = .003) in SMCs after treatment with tumor necrosis factor-alpha. Cellular migration was attenuated by inhibition of CDH11 both with a blocking antibody (0.67 +/- 0.09; P = .063) and gene knockdown mediated by small interfering RNA (0.67 +/- 0.14; P = .036). SMC proliferation decreased by 3.1-fold (P = .006) in the presence of CDH11-blocking antibody. Knockdown of CDH11 mediated by small interfering RNA resulted in a 1.3-fold (P = .018) decrease in proliferation. CONCLUSIONS: CDH11 is up-regulated in SMC in vivo and in vitro as part of the response to injury. Inhibition of CDH11 decreases SMC migration and proliferation, two pathogenic effectors of intimal hyperplasia.
Descriptors: cadherins biosynthesis, cell movement, cell proliferation, muscle, smooth, vascular metabolism, myocytes, smooth muscle metabolism, anastomosis, surgical, antibodies pharmacology, cadherins genetics, cadherins immunology, cell cycle drug effects, cells, cultured, coronary vessels metabolism, coronary vessels physiopathology, dogs, femoral artery surgery, hyperplasia, models, animal, muscle, smooth, vascular drug effects, muscle, smooth, vascular pathology, muscle, smooth, vascular physiopathology, myocytes, smooth muscle drug effects, myocytes, smooth muscle pathology, rna interference, rna, messenger metabolism, rna, small interfering metabolism, time factors, tumor necrosis factor alpha pharmacology, up regulation, veins metabolism, veins physiopathology, veins transplantation.

Mori, E., H. Ikeda, N. Haramaki, T. Ueno, and T. Imaizumi (1997). **Oxidative stress due to no-peroxynitrite pathway is involved in a canine model of myocardial stunning**. *Journal of the American College of Cardiology* 29(2 SUPPL. A): 129A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, animal model, d arginine, ischemia, l arginine, lipid peroxidation marker, malondialdehyde, myocardial stunning, nitric oxide peroxynitrite pathway, nitrotyrosine, oxidative stress, vascular disease.

Morita, H., D.P. Zipes, S.T. Morita, and J. Wu (2007). **Mechanism of U wave and polymorphic ventricular tachycardia in a canine tissue model of Andersen-Tawil syndrome.** *Cardiovascular Research* 75(3): 510-8. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: OBJECTIVE: Andersen-Tawil syndrome (ATS) is a channelopathy affecting inward rectifier potassium I(K1) with QT prolongation, large U waves, and frequent ventricular tachycardia (VT). Although ATS is clinically defined and genetically identified, its electrophysiological mechanism is still unclear, and thus, was the subject of the current study. METHODS AND RESULTS: We replicated the major electrophysiological features of ATS with cesium chloride (CsCl, at I(K1) blockade concentration of 5-10 mmol/l) in 23 isolated

canine left ventricular tissues perfused arterially with Tyrode's solution having normal or low potassium concentrations, [K(+)](o). We mapped action potentials (APs) on the cut-exposed transmural surface of the wedges in control, after CsCl, and CsCl with 0.15 mumol/l isoproterenol (CsCl+ISP). CsCl delayed late phase 3 repolarization and prolonged the duration of the AP, more so during low [K(+)](o) perfusion. Rapid pacing induced delayed afterdepolarizations (DADs) in all low [K(+)](o) and in 71% of normal [K(+)](o) preparations after CsCl treatment. Addition of ISP induced DADs in all preparations. DADs originated in mid-to-endocardium, and initiated VT after CsCl+ISP. Migration of DAD-VT foci resulted in multifocal VT. Alternating DADs at 2 foci resulted in bidirectional VT. There were more foci and longer durations of VT at low [K(+)](o) than at normal [K(+)](o). Delayed late phase 3 repolarization of APs and DADs generated U waves. Verapamil abolished all DADs and VT. CONCLUSIONS: CsCl blockade of I(K1) produced a ventricular wedge model of ATS. Suppressing I(K1) generated U waves by delaying late repolarization of APs and creating DADs, and promoted polymorphic VT by triggering DADs at multiple shifting sites.
Descriptors: andersen syndrome physiopathology, heart conduction system physiopathology, action potentials drug effects, adrenergic beta agonists pharmacology, andersen syndrome metabolism, calcium metabolism, calcium channel blockers pharmacology, cesium, chlorides, dogs, electrocardiography, endocardium metabolism, endocardium physiopathology, heart conduction system drug effects, isoproterenol pharmacology, models, animal, potassium metabolism, potassium channels drug effects, potassium channels metabolism, tissue culture techniques, verapamil pharmacology.

Morita, H., G. Suzuki, T. Mishima, P.A. Chaudhry, P.V. Anagnostopoulos, E.J. Tanhehco, V.G. Sharov, S. Goldstein, and H.N. Sabbah (2002). **Effects of long-term monotherapy with metoprolol cr/xl on the progression of left ventricular dysfunction and remodeling in dogs with chronic heart failure.** *Cardiovascular Drugs and Therapy* 16(5): 443-449. ISSN: 0920-3206.
NAL Call Number: RM345
Abstract: We examined the effects of long-term monotherapy with the beta-blocker, metoprolol controlled release/extended release (CR/XL), on the progression of LV dysfunction as well as on global and cellular remodeling in dogs with heart failure (HF). Chronic HF was produced by intracoronary microembolizations that were discontinued when LV ejection fraction (EF) was between 30% and 40%. Dogs were randomized to 3 months oral monotherapy with metoprolol CR/XL (100 mg once daily, n=7) or no therapy at all (control, n=7). In control dogs, EF decreased from 38+-1% to 31+-2% (p=0.002), and LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) increased (37+-2 vs 45+-2 ml, p=0.001; 59+-3 vs 65+-3 ml, p=0.001; respectively) during the 3 month follow-up period. In dogs treated with metoprolol CR/XL, EF increased after 3 months from 36+-1% to 43+-1% (p=0.001), and ESV decreased (42+-2 vs 38+-2 ml, p=0.003), whereas EDV remained unchanged. Compared to controls, treatment with metoprolol CR/XL showed 46% reduction in replacement fibrosis, 54% reduction in interstitial fibrosis and 20% reduction in myocyte cross-sectional area, a measure of myocyte hypertrophy. These findings indicate that metoprolol CR/XL improves LV function and attenuates progressive global and cellular LV remodeling in dogs with HF. The benefits are fully attributable to beta-blockade alone as no other adjunctive therapy was used.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, chronic heart failure, heart disease, left ventricular dysfunction, heart disease, drug therapy.

Morita, S.T., D.P. Zipes, H. Morita, and J. Wu (2007). **Analysis of action potentials in the canine ventricular septum: no phenotypic expression of M cells.** *Cardiovascular Research* 74(1): 96-103. ISSN: 0008-6363.

NAL Call Number: QM178.A1C38

Abstract: OBJECTIVE: Transmural heterogeneity in the ventricular free wall, enhanced by the midmyocardial long action potential duration (APD) of M cells, plays an important role in the arrhythmogenesis of long QT syndrome. Although we observed dynamic expression of M cell phenotypes in the canine ventricular free wall, it is still unclear whether similar phenomena are present in the interventricular septum. This study evaluated transmural heterogeneity of APD in the septum. METHODS: We isolated and perfused 22 canine septal preparations through the septal branch of the anterior descending coronary artery, and optically mapped 256 channels of action potentials on their cut-exposed transseptal surfaces before and after treatment with sotalol (I(Kr) blocker), anemone toxin II (ATX-II, which slows the inactivation of I(Na)), or drug-free state in 6, 9, and 22 preparations, respectively. The preparations were paced from the left ventricular endocardium at cycle lengths of 500, 1000, 2000, and 4000 ms. RESULTS: We observed progressively lengthening of APD across the septum from the right ventricular to the left ventricular endocardium without a midmyocardial maximum under all conditions. All action potentials had minor phase-1 notches, resembling the endocardial action potential in the ventricular free wall. Increasing cycle lengths and concentrations of sotalol and ATX-II prolonged APD without midmyocardial preference and increased the transseptal dispersion of APDs. CONCLUSIONS: Canine interventricular septal action potentials are similar in shape to the endocardial action potentials in the ventricular free wall, with smooth transseptal transition in APD. We found no phenotypical expression of M cells in the canine interventricular septum.

Descriptors: action potentials physiology, heart conduction system physiology, heart septum physiology, action potentials drug effects, adrenergic beta antagonists pharmacology, cardiotonic agents pharmacology, cnidarian venoms pharmacology, dogs, endocardium physiology, heart septum drug effects, heart septum physiopathology, heart ventricles, long qt syndrome physiopathology, models, animal, perfusion, sotalol pharmacology.

Morris, T.A., J.J. Marsh, P.G. Chiles, R.G. Konopka, C.A. Pedersen, P.F. Schmidt, and M. Gerometta (2004). **Single photon emission computed tomography of pulmonary emboli and venous thrombi using anti-d-dimer**. *American Journal of Respiratory and Critical Care Medicine* 169(9): 987-993. ISSN: 1073-449X.

NAL Call Number: RC705 .A4

Abstract: Previous attempts to diagnose thromboemboli using radiolabeled antibodies and nuclear medicine imaging have been disappointing. We present the results of experiments with intravenous technetium-99m-labeled deimmunized antifibrin Fab' fragments to diagnose thromboemboli using single photon emission computed tomography (SPECT), a highly sensitive scintigraphic imaging technique. Pulmonary emboli (PEs) and lower extremity deep vein thrombi (DVTs) were formed in five dogs, then technetium-99m-labeled Fab'

(dollar sign 400 mg, dollar sign 260 MBq) were injected via forelimb veins. Thoracic and lower extremity SPECT scans were performed at 2-hour intervals after antibody infusion to visualize the thromboemboli. Four hours after antibody infusion, all PEs and DVTs of mass 0.4g or greater were clearly visualized on SPECT scans as 'hot spots' within the lungs and legs, respectively. PEs (0.48 +/- 0.09 g) were intensely radiolabeled, yielding clot/blood radioactivity ratios of 22.8 +/- 5.6. DVTs (0.45 +/- 0.31 g) also had high clot/blood ratios (11.7 +/- 2.6). Infusion of these radiolabeled antibody fragments, combined with SPECT, produces clear images of PEs and DVTs within a clinically feasible time frame. The technique reliably identified even peripheral thromboemboli of relatively small size, which are difficult to diagnose with currently available imaging techniques, and may enable imaging of PEs, DVTs, or both in the same patient.

Descriptors: cardiovascular medicine, human medicine, medical sciences, pulmonary medicine, human medicine, radiology, medical sciences, deep vein thrombosis, vascular disease, pulmonary emboli, respiratory system disease, venous thrombi, vascular disease, venous thromboembolism, single photon emission computed tomography, spect, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques.

Morris, T.A., J.J. Marsh, R. Konopka, C.A. Pedersen, and P.G. Chiles (2004). **Improved imaging of deep venous thrombi during anticoagulation using radiolabelled anti-d-dimer antibodies**. *Nuclear Medicine Communications* 25(9): 917-922. ISSN: 0143-3636.

Abstract: Objectives Radiolabelled anti-fibrin antibodies have not yet enabled reliable and practical diagnosis of venous thromboembolism. However, previous unsuccessful clinical trials were performed with anti-fibrin P-chain antibodies that do not optimally bind to thrombi during anticoagulation. The current experiments were performed to determine if radiolabelled anti-D-dimer antibodies more reliably allowed nuclear medicine imaging of deep venous thrombi during anticoagulation than anti-beta-chain antibodies. Methods Dogs with pre-existing unilateral femoral vein thrombi were anticoagulated with heparin (300 units-kg bolus followed by 90 units.kg-1 .h-1 continuous infusion). They were then allocated to receive one of three 111In labelled antibodies: anti-D-dimer, anti-beta or a non-specific control antibody. Gamma scans of the legs were performed at regular intervals for 24 h. Scans were interpreted in a blinded fashion and the number of gamma counts from the femoral area on the thrombosed side was compared to the contralateral side. Clot/blood isotope density ratios were determined post-mortem. Results Leg thrombi were 100% detectable in the anti-D-dimer group, but only 60% detectable in the anti-beta group. Mean +/- SD relative counts in the thrombosed femoral area was 137 +/- 10% compared to the contralateral side in the anti-D-dimer group, but only 116 20% in the anti-P group. The clot/blood ratio was 24.5 +/- 2.8 in the anti-D-dimer group, but only 7.8 +/- 2.0 in the anti-beta group. Conclusions 111In labelled anti-D-dimer provides superior nuclear medicine images of thrombi during intensive anticoagulation compared to anti-beta. Clinical results with radiolabelled anti-D-dimer may be more promising than those previously observed with other anti-fibrin antibodies. Copyright 2004 Lippincott Williams & Wilkins.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, femoral vein thrombosis, vascular disease, diagnosis, drug therapy, gamma scan, imaging and microscopy techniques, laboratory techniques, indium 111 labelled anti d dimer antibody imaging, clinical techniques, diagnostic techniques.

Mousa, A., J. Bernheim, R. Dayal, S. Hollenbeck, M. Prince, P. Henderson, C. Kent, and P. Faries (2004). **Implication of type ii endoleak on intra-aneurysmal pressure (canine model).** *FASEB Journal* 18(4-5): Abst. 150.1. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, abdominal aortic aneurysm, vascular disease, aneurysm rupture, aneurysmal sac pressure, intra aneurysmal pressure, systemic pressure, type ii endoleak.

Nagueh, S.F., L. Rao, J. Soto, K.J. Middleton, and D.S. Khoury (2004). **Haemodynamic insights into the effects of ischaemia and cycle length on tissue doppler-derived mitral annulus diastolic velocities.** *Clinical Science (London)* 106(2): 147-154. ISSN: 0143-5221.
NAL Call Number: RB37.C43
Abstract: In the present study, we performed simultaneous epicardial echocardiography and left heart catheterization on ten adult dogs to investigate the effects of ischaemia and tachycardia on the mitral annulus early (Ea) and late (Aa) diastolic velocities and the haemodynamic mechanisms involved. Left atrial pressure and left ventricular (LV) volumes and pressures were measured with 5 French Millar catheters. In each dog, inferior vena cava occlusion was used to alter preload and circumflex coronary artery occlusion was applied to induce ischaemia at two different cycle lengths: 450 and 550 ms. At both cycle lengths, ischaemia resulted in a reduction in LV relaxation, LV global and ipsilateral systolic function, transmitral pressure gradient (TMG), Ea and Aa ($P<0.05$). The shorter cycle length was associated with a shorter tau (time constant of LV relaxation), reduced TMG and reduced septal and lateral Ea ($P<0.05$ for all variables). Both septal and lateral Aa were significantly increased ($P<0.05$). Ischaemia influences Ea through changes in LV relaxation, global and regional systolic function and TMG. An increase in heart rate reduces Ea, but increases Aa.
Descriptors: cardiovascular system, transport and circulation, myocardial ischemia, heart disease, vascular disease, diagnosis, tachycardia, diagnosis, epicardial echocardiography, diagnostic techniques, laboratory techniques, left heart catheterization, tissue doppler imaging, imaging and microscopy techniques.

Nagueh, S.F., L.A.R.A. Rao, J. Soto, K.J. Middleton, and D.S. Khoury (2002). **Hemodynamic mechanisms that account for the variable effect of preload on tissue doppler early diastolic velocity.** *Circulation* 106(19 Supplement): II.466. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, ischemia, vascular disease, myocardial dysfunction, heart disease, 5f millar catheter, laboratory equipment, echocardiography, laboratory techniques, left heart catheterization, experimental surgical techniques, tissue doppler imaging, imaging and microscopy techniques, contractility, early diastolic velocity, end systolic force, end systolic pressure, end systolic volume, hemodynamic mechanisms, late systolic load, transmitral pressure gradient.

Naito, M., X.P. Yang, and S. Chiba (2004). **Modification of transmitter release from periarterial nerve terminals by dipyridamole in canine isolated splenic artery.** *Clinical and Experimental Pharmacology and Physiology* 31(3): 185-189. ISSN: 0305-1870.
Abstract: 1. The aim of the present study was to determine the modulatory effects of dipyri-

damole on purinergic and adrenergic transmission in the canine isolated, perfused splenic artery. 2. Periarterial nerve electrical stimulation readily induced a double-peaked vasoconstriction consisting of an initial transient, predominantly P2X receptor-mediated constriction followed by a prolonged, mainly alpha1-adrenoceptor-mediated response. 3. Exposure of tissues to dipyridamole (0.1-1 mumol/L) dose-dependently inhibited both the first and second peaks of the vasoconstrictor response at a low frequency of stimulation (1 Hz), whereas at an intermediate frequency of stimulation (4 Hz), the first peak of the response was depressed without any significant effect being observed on the second peak of constriction. 4. At a higher dose (1 mumol/L) dipyridamole potentiated vasoconstrictor responses to noradrenaline (0.03-1 nmol). At any doses used, dipyridamole had no effect on the vasoconstrictor responses to ATP (0.03-1 mumol). 5. Tyramine (0.01-0.3 mumol) induced vasoconstriction in a dose-dependent manner. The dose-response curves for tyramine were shifted to the right following treatment with dipyridamole (0.1-1 mumol/L). 6. The present results indicate that dipyridamole may inhibit purinegic and adrenergic transmission presynaptically, whereas postsynaptically dipyridamole may potentiate the adrenergic vascular constriction by inhibition of transmitter uptake.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, cotransmission, neuronal vasoconstrictor response, transmitter release modification.

Nakamura, R. and K. Egashira (2001). **Hmg-coa reductase inhibitor pravastatin ameriolates left ventricular dysfunction through inhibition of oxidative stress and inflammation in a canine model of tachycardia-induced heart failure**. *Circulation* 104(17 Supplement): II.247. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, heart failure, left ventricular dysfunction, heart disease, myocardial inflammation, heart disease, tachycardia, disease progression, left ventricular ejection fraction, left ventricular end diastolic pressure, oxidative stress, meeting abstract.

Nattel, S. (2007). **The heart on a chip: the role of realistic mathematical models of cardiac electrical activity in understanding and treating cardiac arrhythmias.** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 4(6): 779-80. ISSN: 1547-5271.
Descriptors: arrhythmias, cardiac genetics, electrophysiology, heart ventricles physiopathology, long qt syndrome genetics, sodium channels genetics, arrhythmias, cardiac drug therapy, arrhythmias, cardiac physiopathology, dogs, long qt syndrome physiopathology, models, animal, models, theoretical.
Notes: Comment On: Heart Rhythm. 2007 Jun;4(6):768-78.

Nishida, K., A. Fujiki, K. Mizumaki, M. Sakabe, M. Sugao, T. Tsuneda, and H. Inoue (2004). **Canine model of brugada syndrome using regional epicardial cooling of the right ventricular outflow tract**. *Journal of Cardiovascular Electrophysiology* 15(8): 936-941. ISSN: 1045-3873.
Abstract: Canine Model of Brugada Syndrome. Introduction: Myocardial cooling can induce J point elevation (Osborn wave) as seen on ECG of the Brugada syndrome by activating transient outward current (Ito) and causing a spike-and-dome configuration of the monopha-

sic action potential (MAP) in the ventricular epicardium in isolated canine ventricular wedge preparations. We determined the effect of regional epicardial cooling of the right ventricular outflow tract (RVOT) on surface ECG and ventricular vulnerability in the dog. Methods and Results: In 12 dogs, a cooling device (20-mm diameter) was attached to the RVOT epicardium, and surface ECG, epicardial MAP, and endocardial MAP were recorded. Regional cooling (29.7degreeC +/- 2.2degreeC) elevated the J point from 0.05 +/- 0.06 mV to 0.12 +/- 0.11 mV and induced T wave inversion (from 0.02 +/- 0.12 mV to -0.27 +/- 0.20 mV) in lead V1 in association with "spike-and-dome" configuration of the epicardial MAP. Cooling prolonged MAP duration in the RVOT epicardium from 172 +/- 27 ms to 213 +/- 30 ms (P < 0.01) but not in the RV endocardium and increased transmural dispersion of MAP duration from 9 +/- 8 ms to 44 +/- 21 ms (P < 0.01). Cooling also prolonged the QT interval in lead V1 from 191 +/- 19 ms to 212 +/- 23 ms (P < 0.05), but not in lead V5, and increased spatial dispersion of QT interval from 7 +/- 5 ms to 20 +/- 10 ms (P < 0.01). QT interval in lead V1 correlated positively with MAP duration in the RVOT epicardium (r = 0.75). T wave amplitude in lead V1 correlated inversely with transmural dispersion of MAP duration in the RVOT (r =-0.74). Vagal nerve stimulation accentuated the cooling-induced changes. During cooling, ventricular fibrillation was induced by a single extrastimulus in 2 of 4 dogs, and additional vagal nerve stimulation during isoproterenol administration induced spontaneous ventricular fibrillation in one dog. Conclusion: Localized epicardial cooling of the RVOT could be an in vivo experimental model of Brugada syndrome.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, nervous system, neural coordination, Brugada syndrome, bundle branch block, genetic disease, heart disease, diagnosis, ventricular fibrillation, chemically induced, electrocardiography, ecg, clinical techniques, diagnostic techniques, myocardial cooling, j point elevation, monophasic action potential, spike and dome configuration, ventricular vulnerability.

Nolan, E.R., M.B. Bailie, and N.B. Olivier (2008). **Effect of autonomic blockade on ventricular repolarization shortening: response to behavioral stimulus in paced dogs.** *Autonomic Neuroscience Basic and Clinical* 140(1-2): 66-71. ISSN: 1566-0702.
Abstract: Autonomic tone has been suggested to be a significant determinant of ventricular repolarization duration with both rate dependent and independent effects. Using the His bundle-paced dog, a model that eliminates the need for QT correction factors, we explored the rate-independent effects of sympathetic and parasympathetic blockade on ventricular repolarization shortening following an excitatory stimulus. Six male His bundle-paced beagle dogs were paced at 80 bpm and fitted with jackets, surface ECG electrodes, and radiotelemeters. Dogs were given propranolol, atropine methyl nitrate, or the appropriate control in a four-period crossover design. Doses were based on literature reviews and unpublished pharmacokinetic/pharmacodynamic modeling to provide efficacious beta- and parasympathetic blockade throughout the data collection period. Data collection began at 11 am and concluded at 11 am the following day, with event stimuli provided by investigators entering the room at 5 pm and at 7 am the following morning. One minute of ECG data were sampled every 15 min and these means were averaged to generate hourly means for the 24 hour data collection period. Treatment with atropine attenuated RT interval shortening when compared with the vehicle group at both the 5 pm and 7 am stimulus. In contrast, propranolol was not associated with significant effects on RT interval duration at either time point. These

results suggest that parasympathetic withdrawal is the primary factor responsible during both awake hours (5 pm) and in the transition from deep sleep to the awake state (7 am) in the facilitation of RT interval shortening following an excitatory stimulus. The attenuation of RT interval shortening following atropine treatment may be a direct effect, or an indirect effect requiring an excited state to become evident. The use of a model that eliminates the need to apply correction factors to repolarization indices helps to clarify the role of the autonomic nervous system on ventricular repolarization.

Descriptors: autonomic nervous system physiology, heart innervation, heart physiology, heart rate physiology, heart ventricles innervation, ventricular function, adrenergic beta antagonists pharmacology, atropine pharmacology, autonomic nervous system drug effects, biological clocks drug effects, biological clocks physiology, bundle of his drug effects, bundle of his physiology, circadian rhythm physiology, dogs, electric stimulation, electrocardiography drug effects, heart rate drug effects, membrane potentials drug effects, membrane potentials physiology, models, animal, muscarinic antagonists pharmacology, pacemaker, artificial, parasympathetic nervous system drug effects, parasympathetic nervous system physiology, propranolol pharmacology, sympathetic nervous system drug effects, sympathetic nervous system physiology, time factors.

Nozari, A., P. Safar, S.W. Stezoski, X. Wu, J. Henchir, A. Radovsky, K. Hanson, E. Klein, P.M. Kochanek, and S.A. Tisherman (2004). **Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs.** *Critical Care Medicine.* 32(10): 2110-6. ISSN: 0090-3493.

Abstract: OBJECTIVE: Therapeutic hypothermia during cardiac arrest and after restoration of spontaneous circulation enables intact survival after prolonged cardiopulmonary cerebral resuscitation (CPCR). The effect of cooling during CPCR is not known. We hypothesized that mild to moderate hypothermia during CPCR would increase the rate of neurologically intact survival after prolonged cardiac arrest in dogs. DESIGN: Randomized, controlled study using a clinically relevant cardiac arrest outcome model in dogs. SETTING: University research laboratory. SUBJECTS: Twenty-seven custom-bred hunting dogs (19-29 kg; three were excluded from outcome evaluation). INTERVENTIONS: Dogs were subjected to cardiac arrest no-flow of 3 mins, followed by 7 mins of basic life support and 10 mins of simulated unsuccessful advanced life support attempts. Another 20 mins of advanced life support continued with four treatments: In control group 1 (n = 7), CPCR was with normothermia; in group 2 (n = 6, 1 of 7 excluded), with moderate hypothermia via venovenous extracorporeal shunt cooling to tympanic temperature 27 degrees C; in group 3 (n = 6, 2 of 8 excluded), the same as group 2 but with mild hypothermia, that is, tympanic temperature 34 degrees C; and in group 4 (n = 5), with normothermic venovenous shunt. After 40 mins of ventricular fibrillation, reperfusion was with cardiopulmonary bypass for 4 hrs, including defibrillation to achieve spontaneous circulation. All dogs were maintained at mild hypothermia (tympanic temperature 34 degrees C) to 12 hrs. Intensive care was to 96 hrs. MEASUREMENTS AND MAIN RESULTS: Overall performance categories and neurologic deficit scores were assessed from 24 to 96 hrs. Regional and total brain histologic damage scores and extracerebral organ damage were assessed at 96 hrs.In normothermic groups 1 and 4, all 12 dogs achieved spontaneous circulation but remained comatose and (except one) died within 58 hrs with multiple organ failure. In hypothermia groups 2 and

3, all 12 dogs survived to 96 hrs without gross extracerebral organ damage (p < .0001). In group 2, all but one dog achieved overall performance category 1 (normal); four of six dogs had no neurologic deficit and normal brain histology. In group 3, all dogs achieved good functional outcome with normal or near-normal brain histology. Myocardial damage scores were worse in the normothermic groups compared with both hypothermic groups (p < .01). CONCLUSION: Mild or moderate hypothermia during prolonged CPCR in dogs preserves viability of extracerebral organs and improves outcome.
Descriptors: animal model, hypothermia, cardiac arrest, cardiopulmonary cerebral resuscitation (CPCR), brain histology, improved outcome.

Nozari, A., P. Safar, S. Tisherman, X. Wu, and S.W. Stezoski (2002). **Hypothermia induced during cardiopulmonary resuscitation increases intact survival after prolonged normovolemic cardiac arrest in dogs.** *2002 Annual Meeting of the American Society of Anesthesiologists, Orlando, FL, USA; October 12-16, 2002,*
Abstract: Studies by us and others have documented improved cerebral outcome with mild hypothermia (34degreeC) induced after cardiac arrest (CA) and restoration of spontaneous circulation (ROSC). We hypothesized that in a simulated unresuscitable CA dog model, intact survival can be achieved if hypothermia is induced during prolonged cardiopulmonary resuscitation (CPR) steps A-B-C. Twelve dogs (20-25 kg) were subjected to 3 min of CA no-flow with ventricular fibrillation (VF), followed by 7 min CPR Basic Life Support and 30 min of unsuccessful CPR Advanced Life Support (ALS) with DC countershocks, FiO2 1.0 and epinephrine boluses. Dogs were randomly allocated into two treatment groups: a control group with normothermic VF (n=6, tympanic temperature (Tty) 37.5degreeC throughout) and a hypothermia group (n=6) which received at VF 20 min a venous flush of 20 ml/kg normal saline at 2degreeC followed by veno-venous extra-corporeal blood cooling (cetheters in superior and inferior vena cava) until cardiopulmonary bypass (CPB) was initiated at VF 40 min. ROSC and assisted circulation were with CPB to 4 h and then mild hypothermia (Tty 34degreeC) to 12 h, controlled ventilation to 48 h, and intensive care to 96 h. Outcome was evaluated as overall performance categories (OPC 1 = normal, 2 = moderate disability, 3 = severe disability, 4 = coma, 5 = death); neurologic deficit scores (NDS 0-10% = normal, 100% = brain death); and 96 h perfusion fixation, necropsy, and determination of total and regional brain histologic damage scores (HDS). Lowest Tty in the hypothermia group was 27degreeC (range 26-28degreeC). ROSC was achieved in all 12 dogs. In the control group, 1 dog survived to 96 h but remained comatose (OPC 4); and 5 dogs died during the intensive care period, the majority within 24 h, because of malignant arrhythmias and respiratory failure or vasopressor resistant shock; "best" NDS was 92% (range 92 - 98%). In the hypothermia group, 5 of the 6 dogs survived to 96 h with good neurologic outcome - OPC 1 (P=0.025) and NDS 0% (0-7%). HDS results are pending. In the control group there were renal failure and intestinal mucosal necrosis, severe subendocardial and epicardial hemorrhagic infarctions, and pulmonary infarctions. In the hypothermia group morphologic changes were absent or minimal (one with bilateral hemorrhagic pulmonary consolidations, 2 with mild subendocardial hemorrhage). In conclusion, cooling during CPR attempts in prolonged normovolemic and presently unresuscitable cardiac arrest, as a bridge to prolonged CPB, results in survival with full neurologic recovery. A portable device for veno-venous cooling should be developed.

Descriptors: cardiovascular system, transport and circulation, cardiac arrest, heart disease, epicardial hemorrhagic infarction, pulmonary infarction, respiratory system disease, cardiopulmonary resuscitation, clinical techniques, therapeutic and prophylactic techniques, hypothermia, laboratory techniques.

Ojalvo, A.-G., A. Seralena, R. Vazquez, J.-F. Montequin, N.-S. Vispo, R. Silva, A. Aldama, Y. Puchades, L.-T. Sorell, P. Lopez-Saura, M.-A. Alfonso, R. Simon, A. Ali, A. Seuc, and L. Herrera (2003). **Therapeutic angiogenesis following intramuscular gene transfer of vascular endothelial growth factor 121 in a dog model of hindlimb ischemia.** *Electronic Journal of Biotechnology* 6(3 Cited December 31, 2003) ISSN: 0717-3458.

Abstract: Vascular endothelial growth factor (VEGF), an endothelial cell-specific mitogen, has been shown to promote therapeutic angiogenesis in animal models of critical limb ischemia. Ischemic skeletal muscle is advantageous for taking up and expressing foreign genes transferred as naked plasmid DNA. Accordingly, we investigated the hypothesis that intramuscular administration of naked plasmid DNA encoding the 121-amino acid isoform of VEGF could augment collateral development and tissue perfusion in a dog hindlimb ischemia model. Unilateral hindlimb ischemia was surgically induced in Beagle dogs. Ten days later, animals received intramuscular injections of pVEGF121 plasmid directly in the ischemic muscles. Angiogenic effects were evaluated by angiography, calf blood pressure ratio and vasomotor reserve analyses. Thirty days after gene transfer, angiographically recognizable collateral vessels were increased in pVEGF121-treated animals compared with controls. Improvement in perfusion to the ischemic limb was documented by a significantly higher calf blood pressure ratio for pVEGF121 (0.79 +- 0.05) versus controls (0.56 +- 0.14, P<0.01). Vasomotor reserve assay suggested amelioration in blood availability at the microcirculation level in pVEGF121-treated animals. Hematological variables showed no significant modification due to the treatment. Our results suggest that intramuscular gene transfer of VEGF121 may promote therapeutic angiogenesis in critical limb vascular insufficiency.

Descriptors: cardiovascular system, transport and circulation, molecular genetics, biochemistry and molecular biophysics, muscular system, movement and support, hindlimb ischemia, vascular disease, therapy , angiography , imaging and microscopy techniques, laboratory techniques, intramuscular gene transfer, genetic techniques, vasomotor reserve assay, bioassay techniques, blood pressure, therapeutic angiogenesis.

Okada, D.R., G. Johnson, Z. Liu, S.D. Hocherman, B.A. Khaw, and R.D. Okada (2004). **Early detection of infarct in reperfused canine myocardium using 99mtc-glucarate**. *Journal of Nuclear Medicine* 45(4): 655-664. ISSN: 0161-5505.

NAL Call Number: RM845.J78

Abstract: 99mTc-Glucarate is an infarct-avid imaging agent with the potential for very early detection of myocardial infarction. The purposes of this study using a canine model were to determine (a) the time course of 99mTc-glucarate uptake and clearance from necrotic and normal myocardium; (b) the 99mTc-glucarate necrotic-to-normal activity ratio over time; (c) the time course of detectable scan positivity after intravenous administration of the tracer; and (d) the relationship of infarct size determined by triphenyltetrazolium chloride (TTC) staining versus 99mTc-glucarate imaging ex vivo. Methods: A 90-min left circumflex coronary artery (LCx) occlusion was followed by 270 min of reperfusion at 100% baseline flow

in 6 open-chest, anesthetized dogs. 99mTc-Glucarate (555 MBq (15 mCi)) was injected 30 min after reperfusion and was followed by 240 min of gamma-camera serial imaging. Microspheres were injected during baseline, occlusion, tracer injection, and before the dogs were euthanized. Creatine kinase assays were performed to assess developing injury. Ex vivo gamma-camera imaging was performed. Blood flow and tracer activity were determined by well counting. TTC stain was used to mark infarct areas, which were sized using computerized digital planimetry. Results: Hemodynamics demonstrated no significant change from baseline at any time for any parameter except LCx flow, which was significantly depressed during occlusion. The mean infarct size +/- SEM was 10.7% +/- 2% of total left ventricle. Blood 99mTc-glucarate clearance was triexponential and rapid. Qualitative image analysis revealed a well defined hot spot after 30 min, which remained well defined through 240 min after injection (150 and 360 min after occlusion, respectively). Images were quantitatively abnormal with hot spot-to-normal zone activity ratios of gtoreq2:1 within 10 min of tracer administration (130 min after occlusion), reaching 8:1 at 240 min after tracer administration (360 min after occlusion). There was a linear correlation between infarct size determined by 99mTc-glucarate and TTC staining (r = 0.96; slope = 0.87). Conclusion: 99mTc-Glucarate marks acute myocardial infarct very early after occlusion and appears to accurately assess infarct size when compared with TTC staining.
Descriptors: cardiovascular system, transport and circulation, radiology, medical sciences, veterinary medicine, medical sciences, myocardial infarction, heart disease, vascular disease, ex vivo gamma camera imaging, imaging and microscopy techniques, laboratory techniques.

Olivier, N.B., G.E. Eyster, R. Sanders, J. Cheng, G. Bohart, M. Girand, and M. Bailie (2003). **Atrioventricular nodal ablation and his-bundle pacing: an acute canine model for proarrhythmic risk assessment.** *Journal of Cardiovascular Electrophysiology* 14(12): 1356-1360. ISSN: 1045-3873.
Abstract: Introduction: QT interval prolongation following drug exposure is considered a marker for increased risk of drug-induced arrhythmias. QT interval measurements are common components of the safety pharmacology assessment of new therapeutic compounds but are potentially confounded by concurrent changes in heart rate that also alter QT intervals. We describe an anesthetized canine model of AV dissociation with His-bundle pacing that overcomes the confounding effects of a change in heart rate. Methods and Results: Transvenous radiofrequency ablation of the AV node was performed in isoflurane-anesthetized dogs and followed by open chest implantation of bipolar pacing electrodes in the vicinity of the His bundle. Pace rates were adjusted from 50 to 190 in steps of 20 beats/min, holding each step for 30 seconds. At each paced rate, QT intervals were measured manually to the nearest 1 ms to construct paced QT interval-heart rate (QT-HR) relationships. Paired QT-HR relationships using identical ascending ramps of pace rates were compared to paired QT-HR relationships with an ascending and descending pace ramp to evaluate short-term reproducibility and hysteresis effects. For proof of concept, an additional QT-HR relationship was constructed in three dogs after intravenous administration of a compound known to alter QT intervals: one dog received terfenadine (0.48 mg/kg bolus followed by 0.017 mg/kg/min infusion), one dog received quinidine (20 mg/kg), and the third dog received sotalol (1 and 3 mg/kg). Substantial interdog variation was found for QT-HR, although short-term reproducibility was high within one dog (average absolute difference for paired ascending

ramps <5 ms). QT intervals measured during descending paced ramps were generally lower than the value for the corresponding paced rate on an ascending ramp. This hysteretic effect was small, averaging <7 ms over the entire ramp. All test compounds prolonged QT intervals and shifted the QT-HR relationship upward. Maximal QT prolongation was 30 ms for terfenadine, 50 ms for quinidine, and 59 ms for sotalol. Conclusion: AV nodal ablation and His-bundle pacing provide a sensitive animal model to identify acute effects of test compounds on indices of myocardial repolarization such as the QT interval. The model is devoid of confounding effects of changing heart rates while enabling identification of effects of drugs over a wide range of controlled rates.

Descriptors: cardiovascular system, transport and circulation, pharmacology, his bundle pacing, diagnostic techniques, atrioventricular nodal ablation, clinical techniques, therapeutic and prophylactic techniques, qt interval, drug effects, heart rate changes, confounding effects, proarrhythmic risk assessment.

Ollerstam, A., S.A. Visser, G. Duker, T. Forsberg, A.H. Persson, L.B. Nilsson, J.A. Bjorkman, J. Gabrielsson, and A. Al Saffar (2007). **Comparison of the QT interval response during sinus and paced rhythm in conscious and anesthetized beagle dogs.** *Journal of Pharmacological and Toxicological Methods* 56(2): 131-44. ISSN: 1056-8719.

NAL Call Number: QP901.J6

Abstract: INTRODUCTION: The aim of the present study was to compare sensitivity in detecting the drug-induced QT interval prolongation in three dog models: conscious telemetered at sinus rhythm and conscious and anesthetized dogs during atrial pacing. The test substances used represent different chemical classes with different pharmacological and pharmacokinetic profiles. METHOD: Dofetilide and moxifloxacin were tested in all models, whereas cisapride and terfenadine were tested in the conscious telemetered and paced models. All substances were given as two consecutive 1.5-h intravenous infusions (infusions 1 and 2). The individual concentration-time courses of dofetilide, moxifloxacin, and cisapride were linked to the drug-induced effects on the QT interval and described with a pharmacokinetic-pharmacodynamic model to obtain an estimate of the unbound plasma concentrations at steady state that give a 10- and 20-ms drug-induced QT interval prolongation (CE10ms and CE20ms). RESULTS: In the conscious telemetered, conscious paced, and anesthetized dog models, the mean CE10ms values were 1.4, 4.0, and 2.5 nM for dofetilide and 1300, 1800, and 12,200 nM for moxifloxacin. For cisapride, the CE10ms values were 8.0 and 4.4 nM in the conscious telemetered and conscious paced dog models. The drug-induced QT interval prolongation during the last 30 min of infusions 1 and 2 was comparable in the conscious models, but smaller in the anesthetized dog model. Terfenadine displayed a marked delay in onset of response, which could only be detected by the extended ECG recording. DISCUSSION: All dog models investigated detected QT interval prolongation after administration of the investigated test substances with similar sensitivity, except for a lower sensitivity in the anesthetized dogs following moxifloxacin administration. The conscious telemetered dog model was favorable, mainly due to the extended continuous ECG recording, which facilitated detection and quantification of delayed temporal differences between systemic exposure and drug-induced QT interval prolongation.

Descriptors: cardiac pacing, artificial, long qt syndrome physiopathology, sinoatrial node physiopathology, telemetry methods, anesthesia, aza compounds administration and dosage,

aza compounds pharmacokinetics, aza compounds toxicity, cisapride administration and dosage, cisapride pharmacokinetics, cisapride toxicity, consciousness, dogs, dose response relationship, drug, drug evaluation, preclinical methods, electrocardiography methods, ether a go go potassium channels physiology, half life, heart rate drug effects, infusions, intravenous, long qt syndrome chemically induced, models, animal, phenethylamines administration and dosage, phenethylamines pharmacokinetics, phenethylamines toxicity, quinolines administration and dosage, quinolines pharmacokinetics, quinolines toxicity, sinoatrial node drug effects, sulfonamides administration and dosage, sulfonamides pharmacokinetics, sulfonamides toxicity, terfenadine administration and dosage, terfenadine pharmacokinetics, terfenadine toxicity, time factors.

Opthof, T., R. Coronel, F.J. Wilms Schopman, A.N. Plotnikov, I.N. Shlapakova, P.J. Danilo, M.R. Rosen, and M.J. Janse (2007). **Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion.** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 4(3): 341-8. ISSN: 1547-5271.
Abstract: BACKGROUND: The concept that the interval between the peak (T(peak)) and the end (T(end)) of the T wave (T(p-e)) is a measure of transmural dispersion of repolarization time is widely accepted but has not been tested rigorously by transmural mapping of the intact heart. OBJECTIVES: The purpose of this study was to test the relationship of T(p-e) to transmural dispersion of repolarization by correlating local repolarization times at endocardial, midmural, and epicardial sites in the left and right ventricles with the T wave of the ECG. METHODS: Local activation times, activation-recovery intervals, and repolarization times were measured at 98 epicardial sites and up to 120 midmural and endocardial sites in eight open-chest dogs. In four of the dogs, long-term cardiac memory was induced by 3 weeks of ventricular pacing at 130 bpm because previous data suggest that, in this setting, delayed epicardial repolarization increases transmural dispersion. The other four dogs were sham operated. RESULTS: In sham dogs, T(p-e) was 41 +/- 2.2 ms (X +/- SEM), whereas the transmural dispersion of repolarization time was 2.7 +/- 4.2 ms (not significant between endocardium and epicardium). Cardiac memory was associated with evolution of a transmural gradient of 14.5 +/- 1.9 ms (P <.02), with epicardium repolarizing later than endocardium. The corresponding T(p-e) was 43 +/- 2.3 ms (not different from sham). In combined sham and memory dogs, T(p-e) intervals did not correlate with transmural dispersion of repolarization times. In contrast, dispersion of repolarization of the whole heart (measured as the difference between the earliest and the latest moment of repolarization from all left and right ventricular, endocardial, intramural, and epicardial recording sites) did correlate with T(p-e) (P <.0005, r = 0.98), although the latter underestimated total repolarization time by approximately 35%. The explanation for this finding is that parts of the heart fully repolarize before the moment of T(peak). CONCLUSION: T(p-e) does not correlate with transmural dispersion of repolarization but is an index of total dispersion of repolarization.
Descriptors: electrocardiography, heart conduction system physiology, action potentials, analysis of variance, cardiac pacing, artificial, dogs, electrodes, implanted, electrophysiologic techniques, cardiac, endocardium physiology, image processing, computer assisted, linear models, models, animal, models, cardiovascular, pericardium physiology, research design,

ventricular function.
Notes: Comment In: Heart Rhythm. 2007 Aug;4(8):1114-6; author reply 1116-9.

Oyama, M.A., B.J. Bulmer, and D. Sisson (2003). **Estimation of left atrial pressure using doppler tissue imaging in a canine model of valvular insufficiency.** *Journal of the American College of Cardiology* 41(6 Supplement A): 440A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, acute mitral valve regurgitation, heart disease, valvular insufficiency, heart disease, doppler tissue imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, swan ganz catheter, surgical instrument, left atrial pressure estimation, clinical techniques, early mitral inflow velocity, early mitral valve annular velocity.

Pagala, M., M. Vaynblat, S. Karaka, Y. Zhukovskiy, P. Shah, R. Fazylov, and J.N. Cunningham (2004). **Influence of premature ventricular complex on left ventricular pressure in dog heart**. *FASEB Journal* 18(4-5): Abst. 202.12. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, ekg, electrocardiogram, laboratory techniques, qrs complex, excitation contraction coupling, left ventricular pressure, premature ventricular complex.

Pagala, M.K., P. Shah, M. Raval, S. Abrol, and J.N.J. Cunningham (2003). **Changes in superoxide dismutase activity in cerebrospinal fluid and serum during spinal cord ischemia and reperfusion in a dog model.** *FASEB Journal* 17(4-5): Abstract No. 567.9. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: superoxide dismutase (SOD), antioxidant enzyme, free radicals, cardiovascular system, transport and circulation, enzymology, biochemistry and molecular biophysics, nervous system, neural coordination, ischemic spinal cord injury, injury, nervous system disease, vascular disease, pathology, spinal cord ischemia, reperfusion, injury, nervous system disease, vascular disease, pathology, aortic cross clamping, experimental surgical techniques, laboratory techniques.

Pap Szekeres, J., G. Cserni, I. Furka, M. Svebis, T. Cserni, E. Brath, N. Nemeth, and I. Miko (2003). **Transplantation and microsurgical anastomosis of free omental grafts: experimental animal model of a new operative technique in dogs.** *Microsurgery* 23(5): 414-418. ISSN: 0738-1085.
Abstract: Our objective was the elaboration of a new animal model for the free transplantation of an omental flap and the examination of its viability in dogs. The cooled omental flap from the abdomen was freely transplanted to the lateral cervical region, and its blood supply was established with microsurgical anastomoses. The technique was developed in 5 dogs, and short-term survival examinations were later carried out in 3 cases by means of this method. Postoperative viability was assessed by angiography, methylene blue testing, and histology. Of the 3 transplanted grafts, 2 still survived 1 week after the operation. For technical reasons, 1 flap thrombotized. For determination of the viability of the transplanted graft, histology

proved best. Vital reactions, including granulation tissue and angiogenesis, were present on the histological slides. The short-term survival of an omental flap can be ensured with microsurgical transplantation in dogs.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, microsurgical anastomosis, experimental surgical techniques, laboratory techniques, omental flap transplantation, experimental surgical techniques, histology.

Patel, C. and C. Antzelevitch (2008). **Cellular basis for arrhythmogenesis in an experimental model of the SQT1 form of the short QT syndrome.** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 5(4): 585-90.
Abstract: BACKGROUND: Short QT syndrome (SQTS) is a primary electrical disease of the heart associated with a high risk of sudden cardiac death. A gain-of-function in I(Kr), due to a mutation in KCNH2, underlies SQT1. OBJECTIVE: This study sought to examine the cellular basis for arrhythmogenesis in an experimental model of SQT1 created using PD-118057, a novel I(Kr) agonist. METHODS: Transmembrane action potentials were simultaneously recorded from epicardial, M, and endocardial regions of arterially perfused canine left ventricular (LV) wedge preparations, together with a pseudo-electrocardiogram. RESULTS: PD-118057 (10 micromol/l) abbreviated the QT interval from 267 +/- 4 to 232 +/- 4 ms and increased transmural dispersion of repolarization (TDR) from 33.7 +/- 2.0 to 49.1 +/- 3.1 ms (P <.001). T-wave amplitude increased from 18.0% +/- 1.4% to 23.1% +/- 1.7% of R-wave amplitude (P =.027). Reversing the direction of activation of the LV wall (epicardial pacing) resulted in an increase in QT interval from 269 +/- 5 to 282 +/- 5 ms and an increase in TDR from 34.1 +/- 2.0 to 57.6 +/- 3.3 ms (P <.001) under baseline conditions. PD-118057 abbreviated the QT interval from 282 +/- 5 to 258 +/- 5 ms and produced a proportional decrease in effective refractory period (ERP). TDR increased from 57.6 +/- 3.3 to 77.6 +/- 4.3 ms (P <.001). Polymorphic ventricular tachycardia (pVT) was induced in 10 of 20 preparations with a single S(2) applied to epicardium. Quinidine (10 micromol/l) increased the ERP and QT interval, did not significantly alter TDR, and prevented induction of pVT in 5 of 5 preparations. CONCLUSION: Our results suggest that a combination of ERP abbreviation and TDR amplification underlie the development of pVT in SQT1 and that quinidine prevents pVT principally by prolonging ERP.
Descriptors: anthranilic acids pharmacology, arrhythmias, cardiac physiopathology, death, sudden, cardiac etiology, death, sudden, cardiac pathology, action potentials genetics, anti arrhythmia agents pharmacology, arrhythmias, cardiac genetics, dogs, electrophysiology, endocardium physiopathology, ether a go go potassium channels genetics, heart ventricles physiopathology, membrane potentials, models, animal, models, theoretical, pericardium physiopathology, potassium channels drug effects, quinidine pharmacology, risk factors.
Notes: Comment In: Heart Rhythm. 2008 Apr;5(4):591-2.

Pavcnik, D., R.T. Andrews, Q. Yin, B.T. Uchida, H.A. Timmermans, C. Corless, N. Toyota, M. Nakata, J. Kaufman, F.S. Keller, and J. Rosch (2003). **A canine model for studying endoleak after endovascular aneurysm repair.** *Journal of Vascular and Interventional Radiology* 14(10): 1303-10. ISSN: 1051-0443.
Abstract: PURPOSE: The aim of this study was to create an animal model of endoleak after stent-graft placement for abdominal aortic aneurysm (AAA) in which a large aneurysmal sac

would be preserved for the testing of techniques for its percutaneous occlusion. MATERIALS AND METHODS: Infrarenal AAAs were created in nine dogs by anastomosis of an isolated segment of the inferior vena cava to the right side of the abdominal aorta in combination with a large anterior patch from the external jugular vein. One hour later, animals underwent percutaneous implantation of polytetrafluoroethylene-covered Z stent endografts with three 3-mm-diameter holes through the fabric. Aortograms were obtained before and after surgery, after endograft placement, and at the time of animal sacrifice at 1 week or 1, 2, 3, or 6 months. Pressures within the aorta and the aneurysm sac were recorded before animal sacrifice. Gross and histologic evaluations of the specimens were then carried out. RESULTS: Immediately after endograft placement, all nine animals had artificial type III endoleaks with angiographic filling of lumbar arteries and veins. One animal died of surgical complications within 2 days of surgery and is not included in our data analysis. One aneurysm ruptured at 1 week. At completion of the study, six endografts were patent and two were occluded. The aneurysm sac had enlarged by approximately 50% in seven animals. At follow-up, type I endoleak was present in three animals, type II endoleak was present in three, and the artificial type III endoleak was present in all six animals with patent endografts. The pressure differential between aorta and aneurysm sac was 36 mm Hg, with a mean aortic pressure of 87 mm Hg +/- 13.3 and a mean aneurysmal sac pressure of 51 mm Hg +/- 28.1. The aneurysmal sac exhibited early thrombus formation at 1 week, which progressed to complete thrombosis in 1-6 months. CONCLUSIONS: The model is technically feasible but would be useful in testing occlusive techniques for residual aneurysm sacs only in the acute phase after endograft placement. It would be not reliable for chronic evaluation because of rapidly progressive thrombosis in most aneurysm sacs and occasional complete thrombosis of the AAA and endograft.
Descriptors: animal model, endoleak, abdominal aortic aneurysm, polytetrafluoroethylene-covered Z stent endografts .

Phillips, S.J., A.B. Kantrowitz, G. Zorzi, L. Zoireff, D. Jaron, P. Freed, and P. Cascade (2007). **Experimental intraaortic balloon pumping prior to acute myocardial infarction. 1973.** *Journal of Extra Corporeal Technology* 39(2): 125-8; Discussion 117-8. ISSN: 0022-1058.
Descriptors: heart assist devices history, intra aortic balloon pumping history, myocardial infarction, acute disease, dogs, history, 20th century, models, animal, myocardium, survival analysis.

Pirat, B., D.S. Khoury, C.J. Hartley, L. Tiller, L. Rao, D.G. Schulz, S.F. Nagueh, and W.A. Zoghbi (2008). **A novel feature-tracking echocardiographic method for the quantitation of regional myocardial function: validation in an animal model of ischemia-reperfusion.** *Journal of the American College of Cardiology* 51(6): 651-9.
NAL Call Number: RC681.A1
Abstract: OBJECTIVES: The aim of this study was to validate a novel, angle-independent, feature-tracking method for the echocardiographic quantitation of regional function. BACKGROUND: A new echocardiographic method, Velocity Vector Imaging (VVI) (syngo Velocity Vector Imaging technology, Siemens Medical Solutions, Ultrasound Division, Mountain View, California), has been introduced, based on feature tracking-incorporating speckle and endocardial border tracking, that allows the quantitation of endocardial strain,

strain rate (SR), and velocity. METHODS: Seven dogs were studied during baseline, and various interventions causing alterations in regional function: dobutamine, 5-min coronary occlusion with reperfusion up to 1 h, followed by dobutamine and esmolol infusions. Echocardiographic images were acquired from short- and long-axis views of the left ventricle. Segment-length sonomicrometry crystals were used as the reference method. RESULTS: Changes in systolic strain in ischemic segments were tracked well with VVI during the different states of regional function. There was a good correlation between circumferential and longitudinal systolic strain by VVI and sonomicrometry ($r = 0.88$ and $r = 0.83$, respectively, $p < 0.001$). Strain measurements in the nonischemic basal segments also demonstrated a significant correlation between the 2 methods ($r = 0.65$, $p < 0.001$). Similarly, a significant relation was observed for circumferential and longitudinal SR between the 2 methods ($r = 0.94$, $p < 0.001$ and $r = 0.90$, $p < 0.001$, respectively). The endocardial velocity relation to changes in strain by sonomicrometry was weaker owing to significant cardiac translation. CONCLUSIONS: Velocity Vector Imaging, a new feature-tracking method, can accurately assess regional myocardial function at the endocardial level and is a promising clinical tool for the simultaneous quantification of regional and global myocardial function.
Descriptors: coronary vessels physiopathology, myocardial ischemia physiopathology, myocardial reperfusion, myocardium, blood flow velocity, coronary vessels ultrasonography, dobutamine, dogs, endocardium, models, animal, myocardial ischemia ultrasonography, propanolamines, systole.

Plotnikov, A.N., E.A. Sosunov, J. Qu, I.N. Shlapakova, E.P. Anyukhovsky, L. Liu, M.J. Janse, P.R. Brink, I.S. Cohen, R.B. Robinson, P.J. Danilo, and M.R. Rosen (2004). **Biological pacemaker implanted in canine left bundle branch provides ventricular escape rhythms that have physiologically acceptable rates.** *Circulation* 109(4): 506-512. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Abstract: Background: We hypothesized that administration of the HCN2 gene to the left bundle-branch (LBB) system of intact dogs would provide pacemaker function in the physiological range of heart rates. Methods and Results: An adenoviral construct incorporating HCN2 and green fluorescent protein (GFP) as a marker was injected via catheter under fluoroscopic control into the posterior division of the LBB. Controls were injected with an adenoviral construct of GFP alone or saline. Animals were monitored electrocardiographically for up to 7 days after surgery, at which time they were anesthetized and subjected to vagal stimulation to permit emergence of escape pacemakers. Hearts were then removed and injection sites visually identified and removed for microelectrode study of action potentials, patch clamp studies of pacemaker current, and/or immunohistochemical studies of HCN2. For 48 hours postoperatively, 7 of 7 animals subjected to 24-hour ECG monitoring showed multiple ventricular premature depolarizations and/or ventricular tachycardia attributable to injection-induced injury. Thereafter, sinus rhythm prevailed. During vagal stimulation, HCN2-injected dogs showed rhythms originating from the left ventricle, the rate of which was significantly more rapid than in the controls. Excised posterior divisions of the LBB from HCN2-injected animals manifested automatic rates significantly greater than the controls. Isolated tissues showed immunohistochemical and biophysical evidence of overexpressed HCN2. Conclusions: A gene-therapy approach for induction of biological pacemaker activity within the LBB system provides ventricular escape rhythms that have physiologically accept-

able rates. Long-term stability and feasibility of the approach remain to be tested.
Descriptors: cardiovascular system, transport and circulation, molecular genetics, biochemistry and molecular biophysics, veterinary medicine, medical sciences, ventricular tachycardia, heart disease, electrocardiography, clinical techniques, diagnostic techniques, gene therapy, clinical techniques, genetic techniques, laboratory techniques, therapeutic and prophylactic techniques, immunohistochemistry, immunologic techniques, laboratory techniques, patch clamp, histology and cytology techniques, action potential, biological pacemaker, heart rate, sinus rhythm, ventricular escape rhythms.

Potse, M., P.F.H.M. Van Dessel, A.C. Linnenbank, C.A. Grimbergen, N.M. Van Hemel, and J.M.T. De Bakker (2004). **Properties of unipolar electrograms recorded with a multielectrode basket catheter.** *Journal of Electrocardiology* 37(1): 1-10. ISSN: 0022-0736.
Abstract: In the past few years, clinical trials with multielectrode "basket" catheters have provided unique recordings from the endocardium of intact in-situ human hearts. Analysis of these recordings is difficult because unipolar electrograms obtained from a basket catheter in the blood-filled cavity differ from those obtained by other mapping techniques such as endocardial balloons used during antiarrhythmic surgery. We investigated these differences using basket catheter recordings obtained in isolated porcine and canine hearts that could be filled with perfusion fluid and evacuated at will. The results indicated that the differences between basket and balloon recordings are largely attributable to the presence and absence of blood. Activation maps obtained in the presence and absence of blood were usually similar and only differed in a minority of cases at sites in which electrograms revealed multiple deflections. In conclusion, unipolar mapping using a basket catheter can be used with confidence for the creation of activation maps if appropriate care is taken in the interpretation of fractionated electrograms.
Descriptors: cardiovascular system, transport and circulation, endocardial mapping, laboratory techniques, multielectrode basket catheter, laboratory equipment, unipolar electrogram recording, activation map.

Prasad, K., J.B. Gupta, J. Kalra, P. Lee, S.V. Mantha, and B. Bharadwaj (1996). **Oxidative stress as a mechanism of cardiac failure in chronic volume overload in canine model**. *Journal of Molecular and Cellular Cardiology* 28(2): 375-385. ISSN: 0022-2828.
Abstract: We investigated the effects of chronic volume overload in the absence or presence of vitamin E supplements on the cardiac function and contractility, cardiac malondialdehyde (MDA) - a lipid peroxidation product - cardiac antioxidant enzyme activity and antioxidant reserve in canine model. The dogs were divided into three groups of seven dogs each: group I, control; group II, mitral regurgitation (MR) of 4 months duration; and group III, MR of 4 months duration receiving vitamin E (40 U/kg/daily) orally. MR was created by detaching two or more chordae tendinae to raise left atrial pressure to 2.5 to three times normal. MR produced a decrease in the index of myocardial contractility with little change in myocardial function. Decrease in myocardial (left and right ventricles) contractility was associated with an increase in cardiac MDA, and a decrease in cardiac antioxidant reserve and antioxidant enzyme activity. Prevention of volume overload-induced decrease in myocardial contractility by vitamin E was associated with a decrease in cardiac MDA and an increase in cardiac antioxidant reserve and glutathione peroxidase activity towards control levels. Superoxide

dismutase and catalase activity remained depressed in vitamin E-treated group. The results indicate that chronic volume overload decreases the contractility of both right and left ventricles and is associated with oxidative stress in both ventricles. These results support the hypothesis that oxygen free radicals are involved in the chronic volume overload-induced cardiac depression.
Descriptors: animal care, biochemistry and molecular biophysics, cardiovascular system, transport and circulation, cell biology, metabolism.

Pua, E.C., S.F. Idriss, P.D. Wolf, and S.W. Smith (2007). **Real-time three-dimensional transesophageal echocardiography for guiding interventional electrophysiology: feasibility study.** *Ultrasonic Imaging* 29(3): 182-94. ISSN: 0161-7346.
Abstract: At present, there are limited methods of acquiring three-dimensional visualization of cardiac structure and function in real-time during interventional electrophysiology procedures. Images acquired for integration of computerized tomography and magnetic resonance imaging with electroanatomic mapping systems are static and are obtained earlier in time. The purpose of this study was to test the feasibility of real-time three-dimensional transesophageal echocardiography for the guidance of interventional electrophysiological studies. A matrix array transducer with 504 channels operating at 5 MHz in a 1 cm diameter steerable esophageal probe was used in conjunction with a scanner capable of real-time 3D scanning of pyramidal volumes from 65 degrees to 120 degrees at rates up to 30 volumes per second. This device has a spatial resolution of approximately 3 mm at 5 cm depth. The authors acquired real-time three-dimensional images of anatomic landmarks of value for electrophysiological procedures in five closed chest canines. Real-time, three-dimensional ultrasound imaging was also used for visualization and guidance of interventional catheter devices within the canine heart. Real-time three-dimensional images of the atria, pulmonary veins, and coronary sinus were acquired. Real-time 3-D color flow Doppler was employed to confirm patency. Multiple image planes of image volumes and rendered views were used to track catheter position and orientation. Images of left veno-atrial junctions have been confirmed by dissection. This study has demonstrated the feasiblity of using real-time three-dimensional transesophageal echocardiography for guiding interventional electrophysiology. The technology has the potential to fill a niche as an adjunct modality for cost-effective real-time interventional guidance and assessment, providing catheter and pacing lead visualization simultaneously with functional volumetric cardiac imaging.
Descriptors: echocardiography, transesophageal, heart catheterization methods, imaging, three dimensional, ultrasonography, interventional, coronary sinus ultrasonography, dogs, feasibility studies, heart atria ultrasonography, models, animal, pulmonary veins ultrasonography, ultrasonography, doppler, color.

Quail, A., S.A. Mcilveen, D. Cottee, and S.W. White (2003). **Tonic cardiac afferent control of airways blood flow in awake dogs.** *FASEB Journal* 17(4-5): Abstract No. 558.11. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: vagal and sympathetic afferents, cardiovascular system, transport and circulation, nervous system, neural coordination, respiratory system, respiration, aortic pressure, bronchial flow, central venous pressure, heart rate.

Ramakers, C., M.A. Vos, P.A. Doevendans, M. Schoenmakers, Y.S. Wu, S. Scicchitano, A. Iodice, G.P. Thomas, C. Antzelevitch, and R. Dumaine (2003). **Coordinated down-regulation of kcnq1 and kcne1 expression contributes to reduction of iks in canine hypertrophied hearts.** *Cardiovascular Research* 57(2): 486-496. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: Objective: In animal models of hypertrophy, electrical remodeling giving rise to QT prolongation occurs rapidly and is associated with the development of torsade de pointes (TdP) arrhythmias and sudden death. Chronic AV block (CAVB)-induced hypertrophy in dogs has been associated with a reduction in the slow component (IKs) of the delayed rectifier potassium current (Ikappa), which contributes to a prolongation of ventricular repolarization, the development of an acquired form of long QT, and the substrate for triggered activity and TdP. The present study was designed to probe the molecular basis for the decrease in IKs by studying the characteristics of KCNE1 and KCNQ1, the putative genes responsible for formation of the channel. Methods and Results: Using a combination of Northern blot, competitive multiplex PCR and immunoblot assays, we found that CAVB reduces KCNE1 and KCNQ1 RNA in the canine ventricles by 70 and 80%, respectively. Protein levels of KCNE1 and KCNQ1 were reduced by 60 and 50%, respectively. We also demonstrate at the molecular level the basis for inter-ventricular difference in IKs density previously reported in hearts of normal dogs and show the basis for reduction of this difference in the CAVB dog. Conclusions: Our results indicate that the CAVB-induced reduction in IKs is due to a down-regulation of KCNE1 and KCNQ1 transcription. The data suggest that electrical remodeling of the cardiac ventricle during hypertrophy involves regulation of the gene expression through modulation of transcriptional and translational regulatory pathways. The reduction in KCNE1 and KCNQ1 expression increases the dependence of ventricular repolarization on the rapid component of Ikappa and may potentiate the action of Class III antiarrhythmic agents.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, genetics, arrhythmia, heart disease, torsades de pointes, qt prolongation, sudden death.

Riou, L.M., C. Ghezzi, G. Vanzetto, A. Broisat, J.P. Mathieu, R. Bontron, R. Pasqualini, and D. Fagret (2003). **Verapamil does not inhibit 99mtcn-noet uptake in situ in normal or ischemic canine myocardium.** *Journal of Nuclear Medicine* 44(6): 981-987. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Abstract: Bis(N-ethoxy,N-ethyldithiocarbamato)nitrido technetium (V) (99mTc) (99mTcN-NOET) is a new myocardial perfusion imaging agent currently undergoing phase III clinical trials in the United States and in Europe. 99mTcN-NOET cellular uptake has been shown to be inhibited by the calcium channel inhibitor verapamil in cultured newborn rat cardiomyocytes. However, the effect of verapamil on in situ 99mTcN-NOET myocardial uptake remains unknown. Therefore, the aim of this study was to evaluate whether the inhibitory effect of verapamil on the cellular uptake of 99mTcN-NOET shown in vitro could be reproduced in situ in a canine model of normal and ischemic myocardium. Methods: 99mTcN-NOET uptake in normal and ischemic myocardium (70% flow reduction in the left anterior descending coronary artery) was measured in the absence or presence of verapamil (0.015 mg/kg/minX10 min) in anesthetized, open-chest dogs (n=17). Control

animals were infused with adenosine (0.2 mg/kg/min) to match the verapamil-induced increase in flow. Results: By verapamil treatment, a clinically relevant plasma concentration of the calcium channel inhibitor was attained (mean+-SEM, 290+-152 ng/mL). In normal myocardium (n=8), regional blood flow at the time of 99mTcN-NOET injection was not statistically different in verapamil- and adenosine-treated dogs (1.69+-0.03 vs. 1.61+-0.04 mL/min/g, respectively). 99mTcN-NOET uptake was slightly higher in the presence of verapamil (0.39+-0.01 vs. 0.38+-0.01 counts per minute (cpm)/(Bq/kg)/g for adenosine; P=0.04). However, no significant difference in 99mTcN-NOET myocardial uptake was observed after normalization of the tracer uptake to regional myocardial blood flow. In ischemic myocardium (n=9), regional blood flow was lower in verapamil-treated than in adenosine-treated animals (0.22+-0.02 vs. 0.29+-0.03 mL/min/g; P<0.05). 99mTcN-NOET uptake in the ischemic area was not inhibited by verapamil (0.09+-0.01 vs. 0.10+-0.01 cpm/(Bq/kg)/g; P=not significant). Conclusion: Verapamil does not inhibit 99mTcN-NOET uptake in situ in normal and ischemic canine myocardium. These results suggest that verapamil should not affect 99mTcN-NOET myocardial uptake in patients referred for myocardial perfusion imaging.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, radiation biology, myocardial ischemia, heart disease, vascular disease.

Rivard, L., H. Sinno, A. Shiroshita Takeshita, G. Schram, T.K. Leung, and S. Nattel (2007). **The pharmacological response of ischemia-related atrial fibrillation in dogs: evidence for substrate-specific efficacy.** *Cardiovascular Research* 74(1): 104-13. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: OBJECTIVE: Acute atrial ischemia produces a substrate for atrial fibrillation (AF) maintenance, but the response of this substrate to antiarrhythmic-drugs has not been defined. The present study assessed the effects of class 1-4 antiarrhythmic-drugs on the electrophysiological consequences of acute atrial ischemia, and compared effects in ischemic AF with those in vagal AF. METHODS AND RESULTS: Isolated atrial ischemia was created by ligating a right coronary artery branch perfusing the right atrial free wall. Experiments were performed in dogs treated with loading and maintenance doses of flecainide (class 1; n=5), nadolol (class 2, n=7), dofetilide (class 3, n=5), or diltiazem (class 4, n=7) prior to coronary artery occlusion. Dogs subjected to coronary occlusion without pre-treatment (n=10) served as controls. Coronary artery occlusion substantially increased AF duration, e.g. from 7+/-4 s (pre-ischemic baseline) to 876+/-245 s at 3 h of ischemia, and caused substantial ischemic zone conduction slowing. Diltiazem and nadolol prevented AF promotion (AF durations 12+/-8 s and 4+/-1 s at 3 h of ischemia respectively; each p<0.001 vs control) and suppressed ischemic conduction slowing. Flecainide and dofetilide failed to prevent ischemia-induced AF promotion (e.g. AF duration at 3-hour ischemia 779+/-417 and 801+/-414 respectively, p=NS vs control) and failed to alter ischemia-induced conduction slowing. A different pattern of response occurred with vagal AF: flecainide was highly effective in reducing vagal AF duration; dofetilide, diltiazem, and nadolol were ineffective. CONCLUSIONS: Beta-blockade and Ca(2+) antagonism suppress the arrhythmic consequences of acute atrial ischemia, whereas Na(+) channel or K(+)-channel block are ineffective. These results are relevant to understanding the effects of different classes of antiarrhythmic-drugs on AF occurring in coronary disease patients.

Descriptors: anti arrhythmia agents therapeutic use, atrial fibrillation prevention and control, coronary disease drug therapy, flecainide therapeutic use, adrenergic beta antagonists therapeutic use, atrial fibrillation etiology, calcium channel blockers therapeutic use, coronary disease complications, diltiazem therapeutic use, dogs, electric stimulation, models, animal, nadolol therapeutic use, phenethylamines therapeutic use, potassium channel blockers therapeutic use, refractory period, electrophysiological drug effects, sodium channel blockers therapeutic use, sulfonamides therapeutic use, vagus nerve.

Rosenthal, D., E.D. Wellons, F.W. Shuler, A.B. Levitt, and V.J. Henderson (2004). **Retrohepatic vena cava and hepatic vein injuries: a simplified experimental methods of treatment by balloon shunt.** *Journal of Trauma Injury Infection and Critical Care* 56(2): 450-452. ISSN: 1079-6061.
Descriptors: cardiovascular system, transport and circulation, digestive system, ingestion and assimilation, methods and techniques, hepatic vein injury, digestive system disease, injury, vascular disease, diagnosis, surgery, retrohepatic vena cava injury, digestive system disease, injury, vascular disease, diagnosis, surgery, balloon shunt, clinical techniques, therapeutic and prophylactic techniques, hepatic lobectomy, experimental surgical techniques, laboratory techniques, risk assessment, survival rate.

Rowell, L.B. (2007). **Human experimentation: no accurate, quantitative data?** *Journal of Applied Physiology* 102(3): 837-40. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Descriptors: cardiovascular physiological phenomena, human experimentation, models, animal, blood volume physiology, body temperature regulation physiology, cats, dogs, exercise physiology, posture physiology, regional blood flow physiology, renal circulation physiology, research design, rheology methods, species specificity.
Notes: Comments: Comment On: J Appl Physiol. 2006 Oct;101(4):1264-5; discussion 1265-6, 1270.

Rozman, J. and S. Ribaric (2007). **Selective recording of electroneurograms from the left vagus nerve of a dog during stimulation of cardiovascular or respiratory systems.** *Chinese Journal of Physiology* 50(5): 240-50. ISSN: 0304-4920.
Abstract: Selective electroneurograms (ENGs) from superficial regions of the left vagus nerve of a dog were recorded with a 33-electrode spiral cuff (cuff) implanted on the nerve at the neck in an adult Beagle dog. The electrodes in the cuff were arranged in thirteen groups of three electrodes (GTE 1-13). To identify the relative positions of the particular nerve regions that innervated the heart and lungs, stimulating pulses (2 mA, 200 micros, 20 Hz) were individually delivered to all thirteen GTEs. It was shown that by delivering stimulating pulses to GTEs 4 and 9, heart rate, blood pressure and respiratory rate were modulated. Precisely, only when the stimuli were delivered to GTE 9, the heart rate began to fall and only when the stimuli were delivered to GTE 4 the rate of breathing decreased. To test the selectivity of recording the above-defined groups GTEs 4 and 9 and randomly chosen GTEs 1 and 7 were simultaneously used as recording GTEs while cardio-vascular or respiratory systems were stimulated by carotid artery compression, epinephrine injection and non-invasive, positive end-pressure ventilation. Results showed that stimulations elicited site-specific changes in

ENG power spectra recorded from the superficial regions of the vagus nerve. Power spectrum of the ENG recorded with GTE 9, contained frequencies belonging to the neural activity elicited by compression of the carotid artery and injection of epinephrine. The power spectrum of the ENG recorded with GTE 4, contained frequencies belonging to the neural activity elicited by non-invasive, positive end-expiratory pressure ventilation. We concluded that the multi-electrode nerve cuff enables selective stimulation and recording of nerve activity from internal organs.

Descriptors: cardiovascular system drug effects, electrodiagnosis instrumentation, electrodiagnosis methods, respiratory system drug effects, vagus nerve physiology, blood pressure drug effects, dogs, electric impedance, electric stimulation, electrodes, electrophysiology, epinephrine pharmacology, heart rate drug effects, models, animal, sensitivity and specificity, vagus nerve anatomy and histology.

Ruiz, M., K. Takehana, F.D. Petruzella, D.D. Watson, G.A. Beller, and D.K. Glover (2002). **Arbutamine stress perfusion imaging in dogs with critical coronary artery stenoses: 99mtc-sestamibi versus 201tl**. *Journal of Nuclear Medicine* 43(5): 664-670. ISSN: 0161-5505.

NAL Call Number: RM845.J78

Abstract: Having previously shown that dobutamine reduces 99mTc-methoxyisobutylisonitrile (sestamibi (MIBI)) uptake in normal myocardium by elevating intracellular calcium, we hypothesized that arbutamine, which has less inotropic effect than dobutamine, might cause less reduction in MIBI uptake, thereby improving defect contrast. In this study using a canine model, we compared the effects of arbutamine stress on myocardial blood flow, myocardial MIBI uptake, and systolic thickening in the presence of a coronary artery stenosis. Methods: Arbutamine was infused (0.5-250 ng/kg/min) in 8 open-chest dogs with critical coronary stenoses that abolished flow reserve. At the time of peak arbutamine effect, MIBI (296 MBq), 201Tl (27.75 MBq), and microspheres were coinjected. The dogs were killed 5 min later, and myocardial tracer activities and flow were quantified by well counting. Ex vivo imaging of heart slices was also performed. Results: Arbutamine increased mean heart rate, peak positive left ventricular pressure and its first time-derivative, and normal-zone myocardial thickening. Stenotic zone flow and thickening did not increase during arbutamine infusion. MIBI uptake versus flow was significantly lower than 201Tl uptake at the same flow values. By imaging, defect magnitude (stenotic/normal) was greater for 201Tl than MIBI (0.56 vs. 0.57; $P<0.001$). Conclusion: In the presence of coronary stenoses that abolished regional flow reserve, myocardial uptake of MIBI, compared with 201Tl, significantly underestimated the arbutamine-induced flow heterogeneity. The attenuation of MIBI uptake and diminished defect contrast during arbutamine stress were comparable with those previously reported for dobutamine stress.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, radiation biology, systolic thickening, heart disease, 201 thallium sestamibi imaging, analytical method, imaging method, 99m technetium sestamibi imaging, arbutamine stress perfusion imaging, defect contrasts, flow reserve, left ventricular pressure, stenotic zone flow.

Saba, D., M. Yilmaz, H. Yavuz, S. Noyan, B. Avci, A. Ercan, H. Ozkan, and M. Cengiz (2007). **Sutureless vascular anastomoses by N-butyl-2 cyanoacrylate adhesive: an experimental animal study.** *European Surgical Research; Europaische Chirurgische Forschung; Recherches Chirurgicales Europeennes* 39(4): 239-44.

Abstract: BACKGROUND: The purpose of this animal study was to find out whether sutureless anastomoses using N-butyl-2-cyanoacrylate were effective in the suppression of neointimal hyperplasia or not. MATERIAL AND METHODS: Ten male adult mongrel dogs were used in this animal study. The animals were randomly divided into a control group (n = 5) and a study group (n = 5). The study group underwent sutureless anastomoses using N-buthyl-2-cyanoacrylate adhesive. Infrarenal aortoaortic graft was interposed using polytetrafluoroethylene. RESULTS: In the study group, the mean intimal thickness at the proximal anastomosis was 27.4 +/- 1.94 microm and 27.4 +/- 1.51 microm at the distal anastomosis. In the control group, the mean intimal thickness was 138.4 +/- 5.02 mum at the proximal anastomosis and 67.6 +/- 6.42 microm at the distal anastomosis. Intimal thickness at the proximal and distal anastomoses in the control group was significantly ($p < 0.001$) greater than in the study group. Also, perianastomotic inflammation was more obvious in the control group compared to the study group ($p < 0.01$). CONCLUSION: Sutureless anastomoses using with N-butyl-2-cyanoacrylate adhesive might be a good alternative to conventional suture technique. Copyright 2007 S. Karger AG, Basel.

Descriptors: anastomosis, surgical methods, aorta surgery, enbucrilate analogs and derivatives, tissue adhesives pharmacology, vascular surgical procedures methods, aorta pathology, dogs, enbucrilate pharmacology, hyperplasia, models, animal, sutures, tunica intima pathology.

Sakuragi, T., Y. Okazaki, M. Mitsuoka, and T. Itoh (2008). **Dramatic hemostasis of the transected pulmonary artery model using SOFT COAG electrosurgical output.** *Interactive Cardiovascular and Thoracic Surgery* 7(5): 764-6.

Abstract: We report the use of low-voltage, automatically regulated, electrosurgical coagulation to seal the bleeding from pulmonary arteries inadvertently during surgical intervention. Conventional electrosurgical coagulation uses high voltage, which generates intensive heat in the tissue. The heat results in carbonized eschar formation that can be easily broken by mechanical stress and lead to postoperative bleeding. SOFT COAG output automatically regulates the output voltage to a maximum of 200 Volts, preventing the generation of sparking. Thus, there is no formation of carbonized eschar. The instrument generates Joule heat alone in the tissue and the temperature rises to below boiling point, which effectively coagulates protein. Initial experiments, using a beagle model, clearly demonstrated the effectiveness and reliability of sealing both macroscopically and histopathologically. SOFT CAOG can be easily adopted both in open thoracotomy as well as in thoracoscopic procedures.

Descriptors: blood loss, surgical prevention and control, electrocoagulation instrumentation, hemostasis, surgical methods, pulmonary artery injuries, pulmonary artery surgery, automation, dogs, equipment design, hemostasis, surgical instrumentation, models, animal, pneumonectomy, pulmonary artery pathology, time factors.

Sander, M., K.L.K. Welling, J.B. Ravn, B. Boberg, and O. Amtorp (2003). **Endogenous no does not regulate baseline pulmonary pressure, but reduces acute pulmonary hypertension in dogs.** *Acta Physiologica Scandinavica* 178(3): 269-277. ISSN: 0001-6772.
NAL Call Number: QP1.A2
Abstract: It has remained unclear whether endogenous production of nitric oxide (NO) plays an important role in the regulation of physiologically normal pulmonary pressures. Severe alveolar hypoxia is accompanied by decreased pulmonary NO production, which could contribute to the development of hypoxic pulmonary hypertension. On the other hand, pharmacological NO inhibition further augments this hypertensive response. Aims: The aims of the present study were to test: (a) whether NO contributes importantly in the maintenance of baseline pulmonary pressure; and (b) to which degree NO is involved in the pulmonary haemodynamic adjustments to alveolar hypoxia. Methods: In anaesthetized dogs (n=37), the systemic and pulmonary haemodynamic effects of the NO synthase inhibitor, Nomega-nitro-L-arginine methyl ester (L-NAME, 20 mg kg-1) and substrate, L-arginine (200-500 mg kg-1), were determined at baseline and during alveolar hypoxia. Constant blood flows were accomplished by biventricular bypass, and systemic normoxaemia was maintained by extracorporeal oxygenation. Results: The primary findings were: (a) L-NAME failed to increase baseline mean pulmonary arterial pressure (10.1+-0.7 vs. 10.5+-0.5 mmHg, P=ns), despite effective NO synthase inhibition as evidenced by robust increases in systemic arterial pressures; (b) L-NAME augmented the pulmonary hypertensive response to alveolar hypoxia (10.2+-0.7 to 19.5+-1.7 with L-NAME vs. 9.9+-1.1 to 15.5+-1.0 mmHg without L-NAME, P<0.05); and (c) L-arginine failed to decrease baseline or elevated pulmonary pressures. Instead, prolonged L-arginine caused increases in pulmonary pressure. Conclusion: These findings suggest that NO plays no significant role in the tonic physiological control of pulmonary pressure, but endogenous NO becomes an important vasodilatory modulator during elevated pulmonary pressure.
Descriptors: cardiovascular system, transport and circulation, respiratory system, respiration, acute pulmonary hypertension, vascular disease, alveolar hypoxia, respiratory system disease, baseline pulmonary pressure.

Satoh, Y., A. Sugiyama, A. Takahara, K. Chiba, and K. Hashimoto (2004). **Electropharmacological and proarrhythmic effects of a class iii antiarrhythmic drug nifekalant hydrochloride assessed using the in vivo canine models**. *Journal of Cardiovascular Pharmacology* 43(5): 715-723. ISSN: 0160-2446.
Abstract: Cardiovascular effects of Nifekalant were examined using halothane-anesthetized dogs, and its proarrhythmic potential was estimated with chronic complete atrioventricular block dogs. Nifekalant was intravenously administered to the halothane-anesthetized dogs in three doses of 0.03, 0.3, and 3 mg/kg/ 10 minutes with a pause of 20 minutes (n = 6). The low dose hardly affected any of the cardiovascular parameters. The middle dose, a clinically recommended antiarrhythmic dose, decreased the total peripheral resistance, increased the cardiac output, and prolonged the ventricular repolarization phase and effective refractory period. The high dose increased the left ventricular contraction, transiently decreased the mean blood pressure, and enhanced the atrioventricular conduction, besides potentiation of the changes induced by the middle dose. Increment in the repolarization phase by the high dose was greater than that in the refractoriness, leading to increase of ventricular electrical

vulnerability. To the atrioventricular block animals, clinically relevant antiarrhythmic dose of 3 mg/kg p.o. of Nifekalant and its 10-times-higher dose were administered. The high dose prolonged QT interval leading to torsades de pointes in all animals (n = 5), which was not detected by the clinical dose (n = 5). These results suggest that antiarrhythmic dose of Nifekalant can be used safely; however, caution should be paid for patients complicating bradycardia and/or a risk of elevated plasma drug concentration.
Descriptors: cardiovascular system, transport and circulation, pharmacology, torsades de pointes, heart disease, atrioventricular conduction, cardiac output, chronic complete atrioventricular block, effective refractory period, left ventricular contraction, mean blood pressure, monophasic action potential, prolonged qt interval, refractoriness, total peripheral resistance, ventricular electrical vulnerability, ventricular repolarization phase.

Satoh, Y., A. Sugiyama, K. Wada, H. Nomura, and K. Hashimoto (2004). **In vivo electropharmacological effects of a class iii antiarrhythmic drug dl-sotalol assessed using halothane anesthetized canine model.** *77th Annual Meeting of the Japanese Pharmacological Society, Osaka, Japan; March 08-10, 2004,*Vol. 94(Supplement 1): 265P,
Descriptors: cardiovascular system, transport and circulation, pharmacology, veterinary medicine, medical sciences, hypotension, vascular disease, blood pressure, left ventricular contraction, ventricular repolarization.

Schneider, A., M. Chandra, G. Lazarovici, I. Vlodavsky, G. Merin, G. Uretzky, J.B. Borman, and H. Schwalb (1997). **Naturally produced extracellular matrix is an excellent substrate for canine endothelial cell proliferation and resistance to shear stress on ptfe vascular grafts**. *Thrombosis and Haemostasis* 78(5): 1392-1398. ISSN: 0340-6245.
Abstract: Purpose: Successful development of a vascular prosthesis lined with endothelial cells (EC) may depend on the ability of the attached cells to resist shear forces after implantation. The present study was designed to investigate EC detachment from extracellular matrix (ECM) precoated vascular prostheses, caused by shear stress in vitro and to test the performance of these grafts in vivo. Methods: Bovine aortic endothelial cells were seeded inside untreated polytetrafluoro-ethylene (PTFE) vascular graft (10 X 0.6 cm), PTFE graft precoated with fibronectin (IN), or PTFE precoated with FN and a naturally produced ECM (106 cells/graft). Sixteen hours after seeding the medium was replaced and unattached cells counted. The strength of endothelial cell attachment was evaluated by subjecting the grafts to a physiologic shear stress of 15 dynes/cm2 for 1 h. The detached cells were collected and quantitated. PTFE or EC preceded ECM coated grafts were implanted in the common carotid arteries of dogs. Results: While little or no differences were found in the extent of endothelial cell attachment to the various grafts (79%, 87% and 94% of the cells attached to PTFE, FN precoated PTFE, or FN+ECM precoated PTFE, respectively), the number of cells retained after a shear stress was significantly increased on ECM coated PTFE (20%, 54% and 85% on PTFE, FN coated PTFE, and FN+ECM coated PTFE, respectively, p <0.01). Implantation experiments in dogs revealed a significant increase in EC coverage and a reduced incidence of thrombus formation on ECM coated grafts that were seeded with autologous saphenous vein endothelial cells prior to implantation. Conclusion: ECM coating significantly increased the strength of endothelial cell attachment to vascular prostheses subjected to shear stress. The presence of adhesive macromolecules and potent endothelial cell

growth promoting factors may render the ECM a promising substrate for vascular prostheses.
Descriptors: cardiovascular system, transport and circulation, equipment apparatus devices and instrumentation, polytetrafluoro ethylene vascular graft, prosthetic, shear stress.

Schwartz, L.M., R.B. Jennings, and K.A. Reimer (1995). **Minimum ischemic stress required for myocardial preconditioning in dogs: effect of analgesia, using the opiate agonist-antagonist, butorphanol.** *FASEB Journal* 9(3): A299. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, pharmacology, meeting abstract, pentobarbital.

Sharifov, O.F., V.V. Fedorov, G.G. Beloshapko, A.V. Glukhov, A.V. Yushmanova, and L.V. Rosenshtraukh (2004). **Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs.** *Journal of the American College of Cardiology* 43(3): 483-490. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Abstract: OBJECTIVES We studied the effects of beta-adrenergic and cholinergic stimulation and blockade on spontaneous atrial fibrillation (AF) in the intact dog heart. BACKGROUND Paroxysmal AF is often preceded by changes in autonomic tone, but the relative roles of adrenergic and cholinergic influences on AF induction are not well known. METHODS Perfusion of catecholamines and acetylcholine (ACh), as well as their combination, through the sinus node artery was used to induce AF in 20 anesthetized open-chest dogs without electrical stimulation of atria. RESULTS Isoproterenol and adrenaline (10 to 100 mumol/l) induced AF in 21% (3 of 14) and 17% (1 of 6) of dogs, respectively. Atropine (1 to 2 mg) treatment prevented catecholamine-mediated AF, indicating a critical role of cholinergic tone in these AF episodes. Acetylcholine (2.8 +- 0.3 mumol/l) induced AF in all dogs. Beta-blockade by propranolol (1 mg/kg) did not prevent ACh-induced AF, but increased the threshold ACh concentration for AF induction to 23.5 +- 3.4 mumol/l ($p < 0.05$). Acetylcholine-mediated AF was facilitated by isoproterenol (1 to 2 and 10 mumol/l), which decreased the threshold ACh concentration for AF induction to 0.5 +- 0.1 and 0.4 +- 0.1 mumol/l, respectively ($p < 0.05$) and increased the AF duration (from 25 +- 7 to 141 +- 54 and 233 +- 60 s, respectively; $p < 0.05$). Epicardial mapping of the right atrium (112 unipolar electrodes) demonstrated similar activation patterns during arrhythmias induced by ACh and catecholamines. CONCLUSIONS These data indicate that although both autonomic systems play a role in AF, cholinergic stimulation is likely the main factor for spontaneous AF initiation in this animal model. Adrenergic tone modulates the initiation and maintenance of cholinergically mediated AF.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology, spontaneous atrial fibrillation, heart disease, adrenergic stimulation, cholinergic stimulation.

Shen, Y.T., J.J. Mallee, L.K. Handt, D.B. Gilberto, J.J.J. Lynch, R.J. Hargreaves, K.S. Koblan, R.J. Gould, and S.A. Kane (2003). **Effects of inhibition of alpha-cgrp receptors on cardiac and peripheral vascular dynamics in conscious dogs with chronic heart failure.** *Journal of Cardiovascular Pharmacology* 42(5): 656-661. ISSN: 0160-2446.

Abstract: Whether endogenous calcitonin gene-related peptide (CGRP) plays a role in heart failure is unclear. Seven dogs were instrumented with left ventricular (LV) pressure gauges, pacers, coronary occluder and aortic, atrial, and coronary sinus catheters. Hemodynamic recordings and response to alpha-CGRP challenge were obtained for baseline in the conscious state. Rapid pacing (240 beats/min) was then initiated. The coronary artery was occluded for 90 minutes followed by reperfusion after 2 weeks of pacing. After 6 weeks of pacing, LV pressure (-11+-6%), LV dP/dt (-53+-5%), and mean arterial pressure (-15+-4%) decreased (P<0.01), while left atrial pressure (+19+-3 mm Hg from 7+-1 mm Hg) and heart rate (+53+-16%) increased (P<0.01). Infusion of the alpha-CGRP receptor antagonist alpha-CGRP(8-37) (30 mug/kg/min, iv), which blocked the exogenous alpha-CGRP challenge, did not affect any of these indices. Regional blood flow, as measured by the microsphere technique, in the nonischemic myocardium, as well as cerebral and renal vasculatures were unaltered during the infusion of alpha-CGRP(8-37). Plasma concentrations of CGRP from both arterial and coronary sinus samples were unchanged after 6 weeks of pacing as compared with control. Thus, we conclude that endogenous alpha-CGRP does not appear to play a major role in the regulation of cardiac and peripheral vascular dynamics in the late stage of heart failure.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, methods and techniques, chronic heart failure, heart disease, cardiac vascular dynamics, peripheral vascular dynamics.

Shi, H., H. Wang, D. Li, S. Nattel, and Z. Wang (2004). **Differential alterations of receptor densities of three muscarinic acetylcholine receptor subtypes and current densities of the corresponding k+ channels in canine atria with atrial fibrillation induced by experimental congestive heart failure.** *Cellular Physiology and Biochemistry* 14(1-2): 31-40. ISSN: 1015-8987.
NAL Call Number: QH573.C455
Abstract: Parasympathetic tone and congestive heart failure (CHF) are two of promoting factors in initiation and perpetuation of atrial fibrillation (AF). Recent studies indicate coexistence of multiple muscarinic acetylcholine receptor Subtypes (mAChRs) that mediate several distinct K+ currents in the heart; inward rectifier K+ current IKACh by the M2, and two delayed rectifier K+ currents IKM3 and IK4AP by the M3 and M4 receptors, respectively. We studied the alterations of atrial mAChRs and their coupled K+ channels in the setting of AF in dogs with ventricular tachypacing-induced CHF. Whole-patch-clamp recordings showed that the current densities of IKACh (induced by 1 mM acetylcholine) and IK4AP (induced by 1 mM 4-aminopyridine) were apprx45% and apprx55% lower, respectively, while that of IKM3 (induced by 10 mM choline) was apprx75% higher, at a plateau voltage of 0 mV in atrial myocytes from CHF than those from healthy hearts. In healthy hearts, IKACh comprised >60%, and IKM3 and IK4AP<30%, of the total outward K+ currents mediated by mAChRs at depolarized potentials (between -20 mV and +50 mV). In AF atria of CHF dogs, however, the contribution of IKM3 increased to apprx50%, exceeding those of IKACh or IK4AP. Western blot analyses with atrial membrane protein samples indicated that receptor densities of the M2 and M4 subtypes decreased by apprx33% and apprx22%, respectively, whereas that of the M3 subtype increased by apprx2.3 folds, in parallel to the alterations of the corresponding K+ currents. We conclude that differential

alterations of mAChR subtypes underlie differential alterations of their coupled K+ channels in AF atria and these differential alterations may contribute to atrial remodeling in AF induced in the setting of CHF.
Descriptors: cardiovascular system, transport and circulation, atrial fibrillation, heart disease, experimental congestive heart failure, western blot, genetic techniques, laboratory techniques, patch clamp recording, histology and cytology techniques.

Shimizu, J., S. Mohri, G. Iribe, Y. Kitagawa, H. Ito, J. Araki, M. Takaki, and H. Suga (2003). **Postextrasystolic contractility normally decays in alternans in canine in situ heart.** *Japanese Journal of Physiology* 53(4): 313-318. ISSN: 0021-521X.
NAL Call Number: QP34.5.J3
Abstract: We have reported that the postextrasystolic (PES) potentiation of left ventricular (LV) contractility usually decays in alternans at heart rates above 80-100 beats/min in the canine excised, cross-circulated heart. We examined whether the PES contractility would also decay in alternans even in the canine in situ heart presumably more physiological than the excised heart. In anesthetized, ventilated, and open-chest mongrel dogs, we measured LV pressure and volume with a micromanometer and a conductance catheter cannulated into the LV and obtained LV end-systolic maximum elastance (Emax) as the reasonably load-independent contractility index. We inserted an extrasystole followed by a compensatory pause into steady-state regular beats at heart rates above 90 beats/min and analyzed the PES decay pattern of Emax. We found that Emax potentiated in the first PES beat decayed in alternans within 5-6 PES beats. This indicates that PES contractility also decays in alternans in the normal canine in situ heart.
Descriptors: cardiovascular system, transport and circulation, arrhythmia, heart disease, alternans decay, calcium recirculation, compensatory pause, left ventricular contractility, postextrasystolic potentiation, left ventricular end systolic maximum elastance, postextrasystolic contractility, pressure volume loop.

Shiroshita Takeshita, A., B.J. Brundel, B. Burstein, T.K. Leung, H. Mitamura, S. Ogawa, and S. Nattel (2007). **Effects of simvastatin on the development of the atrial fibrillation substrate in dogs with congestive heart failure.** *Cardiovascular Research* 74(1): 75-84. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Abstract: BACKGROUND: Congestive heart failure (CHF) is a common cause of atrial fibrillation (AF). Oxidative stress and inflammation (profibrotic) and peroxisome proliferator-activated receptor-alpha (PPAR-alpha, antifibrotic) factors may be involved in CHF-related remodeling. We evaluated the effects of simvastatin (antioxidant, anti-inflammatory) and fenofibrate (PPAR-alpha activator) on CHF-related atrial remodeling. METHODS AND RESULTS: Dogs were subjected to 2-week ventricular tachypacing (VTP) in the absence and presence of simvastatin (20 or 80 mg/day) or fenofibrate. Induced AF duration (DAF) was increased by VTP from 36+/-14 (non-paced controls) to 1005+/-257 s (p<0.01). Simvastatin prevented VTP-induced DAF increases (147+/-37 and 84+/-37 s at 20 and 80 mg/day, respectively), but fenofibrate did not (1018+/-352 s). Simvastatin also attenuated CHF-induced conduction abnormalities (heterogeneity-index reduced from 1.5+/-0.1 to 1.1+/-0.1 and 1.0+/-0.1 at 20 and 80 mg/day, p<0.01) and atrial fibrosis (from

19.4+/-1.3% to 10.8+/-0.8% and 9.9+/-0.8% at 20 and 80 mg/day, p<0.01), while fenofibrate did not. Simvastatin (but not fenofibrate) also attenuated VTP-induced left-ventricular nitric-oxide synthase and nitrotyrosine increases, along with hemodynamic dysfunction. Atrial fibroblast proliferation increased with 24-h fetal bovine serum (FBS) stimulation from 654+/-153 to 7264+/-1636 DPM (p<0.001). Simvastatin, but not fenofibrate, suppressed fibroblast proliferation (664+/-192 DPM, p<0.001). Simvastatin also significantly attenuated transforming growth factor-beta1-stimulated alpha-smooth muscle actin (alpha-SMA) expression (indicating myofibroblast differentiation) from 1.3+/-0.1 to 1.0+/-0.1 times baseline (p<0.05). CONCLUSIONS: CHF-induced atrial structural remodeling and AF promotion are attenuated by simvastatin, but not fenofibrate. Statin-induced inhibition of profibrotic atrial fibroblast responses and attenuation of left-ventricular dysfunction may contribute to preventing the CHF-induced fibrotic AF substrate.
Descriptors: anti inflammatory agents therapeutic use, atrial fibrillation prevention and control, heart failure drug therapy, simvastatin therapeutic use, actins analysis, antilipemic agents therapeutic use, atrial fibrillation etiology, biological markers analysis, cardiac pacing, artificial, cell proliferation drug effects, cells, cultured, dogs, fibroblasts drug effects, heart atria chemistry, heart failure complications, heart ventricles chemistry, models, animal, nitric oxide synthase type ii analysis, nitric oxide synthase type iii analysis, ppar alpha agonists, procetofen therapeutic use, refractory period, electrophysiological drug effects, tyrosine analogs and derivatives, tyrosine analysis, ventricular remodeling drug effects.
Notes: Comment In: Cardiovasc Res. 2007 Apr 1;74(1):8-10.

Silva, G.V., S. Litovsky, J.A.R. Assad, A.L.S. Sousa, B.J. Martin, D. Vela, S.C. Coulter, J. Lin, J. Ober, W.K. Vaughn, R.V.C. Branco, E.M. Oliveira, R. He, Y.J. Geng, J.T. Willerson, and E.C. Perin (2005). **Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model**. *Circulation* 111(2): 150-156. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Abstract: Background - Bone marrow - derived stem cells are under investigation as a treatment for ischemic heart disease. Mesenchymal stem cells (MSCs) have been used preferentially in the acute ischemia model; data in the chronic ischemia model are lacking. Methods and Results - Twelve dogs underwent ameroid constrictor placement. Thirty days later, they received intramyocardial injections of either MSCs (100 x 106 MSCs/10 mL saline) (n = 6) or saline only (10 mL) (controls) (n = 6). All were euthanized at 60 days. Resting and stress 2D echocardiography was performed at 30 and 60 days after ameroid placement. White blood cell count (WBC), C-reactive protein (CRP), creatine kinase MB (CK-MB), and troponin I levels were measured. Histopathological and immunohistochemical analyses were performed. Mean left ventricular ejection fraction was similar in both groups at baseline but significantly higher in treated dogs at 60 days. WBC and CRP levels were similar over time in both groups. CK-MB and troponin I increased from baseline to 48 hours, eventually returning to baseline. There was a trend toward reduced fibrosis and greater vascular density in the treated group. MSCs colocalized with endothelial and smooth muscle cells but not with myocytes. Conclusions - In a canine chronic ischemia model, MSCs differentiated into smooth muscle cells and endothelial cells, resulting in increased vascularity and improved cardiac function.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, ischemic heart disease, therapy, ameroid constrictor placement, laboratory techniques, echocardiography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, left ventricular ejectin fraction.

Sleph, P.G., K.K. Sadanaga, D.E. Burkett, C.S. Parham, R.J. Scalese, and G.J. Grover (2003). **Effect of mitochondrial katp activation on necrosis in an isolated gracilis model of ischemia and reperfusion in dogs.** *FASEB Journal* 17(4-5): Abstract No. 150.5. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, muscular system, movement and support, pharmacology, ischemia reperfusion, reperfusion injury, vascular disease, necrosis.

Spaan, J.A., S. Dekker, D.S. Fokkema, I. Vergroesen, and H. Vink (2001). **Shear stress induced endothelial no release in canine coronary circulation is attenuated by the glycocalyx**. *Circulation* 104(17 Supplement): II.302 II.303. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, blood flow conductance, peak reactive hyperemia, shear stress, meeting abstract.

Stambler, B.S., G. Fenelon, R.K. Shepard, H.F. Clemo, and C.M. Guiraudon (2003). **Characterization of sustained atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure.** *Journal of Cardiovascular Electrophysiology* 14(5): 499-507. ISSN: 1045-3873.
Abstract: Atrial Tachycardia in Heart Failure. Introduction: Atrial arrhythmias often complicate congestive heart failure (CHF). We characterized inducible atrial tachyarrhythmias and electrophysiologic alterations in dogs with CHF and atrial enlargement produced by rapid ventricular pacing. Methods and Results: Endocardial pacing leads were implanted in the right ventricle, right atrium, and coronary sinus in 18 dogs. The right ventricular lead was connected to an implanted pacemaker capable of rapid ventricular pacing. The atrial leads were used to perform electrophysiologic studies in conscious animals at baseline in all dogs, during CHF induced by rapid ventricular pacing at 235 beats/min in 15 dogs, and during recovery from CHF in 6 dogs. After 20 +- 7 days of rapid ventricular pacing, inducibility of sustained atrial tachycardia (cycle length 120 +- 12 msec) was enhanced in dogs with CHF. Atrial tachycardia required a critical decrease in atrial burst pacing cycle length (ltoreq 130 msec) for induction and often could be terminated by overdrive pacing. Calcium antagonists (verapamil, flunarizine, ryanodine) terminated atrial tachycardia and suppressed inducibility. Effective refractory periods at 400- and 300-msec cycle lengths in the right atrium and coronary sinus were prolonged in dogs with CHF. Atrial cells from dogs with CHF had prolonged action potential durations and reduced resting potentials and delayed afterdepolarizations (DADs). Mitochondria from atrial tissue from dogs with CHF were enlarged and had internal cristae disorganization. Conclusions: CHF promotes inducibility of sustained atrial tachycardia. Based on the mode of tachycardia induction, responses to pacing and calcium antagonists, and presence of DADs, atrial tachycardia in this CHF model has a mechanism most consistent with DAD-induced triggered activity resulting from intracellular calcium overload.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, arrhythmia, heart disease, atrial tachycardia, congestive heart failure, rapid ventricular pacing.

Stepp, D.W., Y. Nishikawa, and W.M. Chilian (1999). **Regulation of shear stress in the canine coronary microcirculation**. *Circulation* 100(14): 1555-1561. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Abstract: Background: Physical forces, such as pressure and flow, are well known to affect vascular function in the coronary circulation. Increases in shear stress produce vasodilation in coronary arterioles in vitro, and constant-flow preparations suggest a role for shear stress-induced vasodilation during adjustments to metabolic demand in vivo. Hypothetically, the regulation of shear stress can be viewed as a negative feedback control scheme (increased velocity fwdarw increased shear fwdarw vasodilation fwdarw decreased velocity fwdarw shear normalized). Therefore, we hypothesized that shear stress would be at least partially regulated during conditions of elevated flow. Methods and Results: We used fluorescence microangiography to measure microvascular diameters and velocities in the coronary circulation in vivo and used these variables to calculate shear stress. Measurements were obtained under basal conditions, during maximal coronary blood flow, and after inhibition of NO synthase. Basal shear stress in the coronary circulation averaged 10 dyn/cm2 in small arteries and 19 dyn/cm2 in arterioles. Regulation of shear stress was observed in small arteries during adenosine-induced increases in coronary blood flow, but arterioles showed minimal regulation. NO synthase blockade had no effect on basal shear stress but completely abolished its regulation in small arteries during vasodilation. Conclusions: Our data provide the first quantitative estimates of microvascular shear stress in the coronary circulation. Moreover, our results suggest that shear stress in small coronary arteries is regulated by NO release from the endothelium.
Descriptors: cardiovascular system, transport and circulation, coronary microcirculation, flow force, pressure force, shear stress, nitric oxide release regulated, regulation, vascular function.

Stonerook, M., C. Hassler, P. Tosca, J. Merrill, D. Vasconcelos, and A. Smith (2003). **Cardiotoxicity study of nsc-638850 (ucn-01) and cytostar (ara-c) given alone or in combination to beagle dogs.** *Toxicological Sciences* 72(S-1): 36 ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Descriptors: pharmacology, toxicology, cardiotoxicity, heart disease, toxicity, drug induced, ecg, electrocardiography, clinical techniques, diagnostic techniques, cardiovascular evaluation, combination chemotherapy, therapeutic and prophylactic techniques, blood pressure, body temperature, heart rate, necrosis, vascular resistance, venodilation.

Stuyvers, B.D., P.A. Boyden, and H.E.D.J. Ter Keurs (2004). **2d-confocal analysis of spontaneous micro ca2+-transients in canine purkinje cells.** *Biophysical Journal* 86(1): 223A. ISSN: 0006-3495.
NAL Call Number: 442.8 B5238
Abstract: Aim: Confocal microscopy of Ca2+ using lines positioned longitudinally (LongL) in the core of unstimulated canine Purkinje cells (PCell) have shown typical Ca2+-sparks,

spontaneous cell-wide waves and brief local increases of (Ca2+)i with larger amplitudes and different shapes compared to sparks. Transverse scans of Pcells (TransL) showed Ca2+-elevations propagating from the edge to the core. Our observations suggested that microCa2+ waves move from the edge to the core at varying angles (10-90deg) relative to the sarcolemma. Here, we present an analysis of the 3 dimensional dynamics of these Ca2+ events by using confocal scans at different positions in the cells and 2D-imaging of the initiation and propagation of the waves. Methods: 18 PCell aggregates were isolated from canine hearts, incubated with Fluo4-AM, superfused with Tyrode (25-30degreeC, pH 7.4, Cao=2 mM). Fluorescence of Fluo4 (F) was scanned along 25 mum lines and represented as ratio F/Fo (Fo: basal fluorescence). We visualized local Ca2+-events by confocal images (10mumX-10mum; 8 frames/s). Results: LongL at varied distance from the sarcolemma showed initiation of transverse microwaves in a subsarcolemmal region (subSL: 3 to 8 mum from the sarcolemma). The combination of TransL and LongL revealed Ca2+-events propagating along the sarcolemma in the SubSL. Spark-like Ca2+-events with large amplitude (F/Fo>3) were clearly identified in the subSL. Confocal 2D-imaging of Ca2+ focused on cell edges showed microwaves that propagate within the subSL region (velocity apprx50mum/s). On their path, these SubSL occasionally initiate secondary waves that move toward the core. Conclusion: Our observations suggest a multidirectional system for Ca2+-activation in Pcells. We propose that, in Pcells, which lack t-tubules, a subSL compartment acts as an initiator of micro Ca2+ waves, which triggers major Ca2+ releases in the core compartment.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, nervous system, neural coordination, 2d confocal microscopy, two dimensional confocal microscopy, imaging and microscopy techniques, laboratory techniques.

Sugiyama, A. (2003). **Effects of clinically available drugs on the repolarization process of the heart assessed by the in vivo canine models.** *Folia Pharmacologica Japonica* 121(6): 393-400. ISSN: 0015-5691.
Abstract: The proarrhythmic effects of class III antiarrhythmic agents and non-cardiovascular drugs, which have been shown to prolong QT interval, were assessed using two types of in vivo canine models. First, electrophysiological effects of dofetilide, nifekalant, amiodarone, cisapride, astemizole, sulpiride, haloperidol, and sparfloxacin were assessed using halothane-anesthetized dogs. Each drug prolonged the monophasic action potential (MAP) duration and effective refractory period (ERP) at clinically recommended daily doses. The extent of increase was greater in the refractoriness than in the repolarization only for amiodarone, indicating abbreviation of the terminal repolarization period. The reverse was true for the other drugs. Next, torsadogenic action of sematilide, nifekalant, amiodarone, cisapride, terfenadine, sulpiride, and sparfloxacin was assessed using chronic complete atrioventricular block dogs with Holter ECG monitoring in the conscious state. Oral administration of 1-10 times higher doses than the clinically relevant doses of the drugs induced polymorphic ventricular tachycardia torsades de pointes (TdP), except for amiodarone. These results indicate that the prolongation and backward shift of the terminal repolarization period may be closely related to the drug-induced TdP and suggest that these in vivo models can be used to screen proarrhythmic potential of new drugs.
Descriptors: cardiovascular system, transport and circulation, pharmacology, veterinary medicine, medical sciences, atrioventricular block, heart block, long QT syndrome, polymor-

phic ventricular tachycardia, heart disease, torsades de pointes, holter ecg monitoring, holter electrocardiography monitoring, clinical techniques, diagnostic techniques, qt interval, effective refractory period [erp], monophasic action potential.
Language of Text: Japanese.

Sugiyama, A., Y. Satoh, K. Wada, H. Nomura, Y. Nakamura, and K. Hashimoto (2004). **Torsadogenic action of qt-prolonging drugs, astemizole and haloperidol, assessed by the canine chronic atrioventricular block model.** *Journal of Pharmacological Sciences* 94(Supplement 1): 151P. ISSN: 1347-8613.
Descriptors: cardiovascular system, transport and circulation, pharmacology, torsades de pointes, heart disease, toxicity, drug induced, pathology, ventricular fibrillation, holter ecg monitoring, holter electrocardiography monitoring, clinical techniques, intravenous administration, oral administration, clinical techniques, chronic atrioventricular block, effective refractory period, idioventricular automaticity, ventricular repolarization phase.

Swissa, M., S. Zhou, I. Gonzalez Gomez, C.M. Chang, A.C. Lai, A.W. Cates, M.C. Fishbein, H.S. Karagueuzian, P.S. Chen, and L.S. Chen (2004). **Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death.** *Journal of the American College of Cardiology* 43(5): 858-864. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Abstract: OBJECTIVES: We sought to develop a high-yield canine model of sudden cardiac death (SCD). BACKGROUND: Because electrical stimulation is a powerful means to elicit nerve sprouting, we hypothesize that subthreshold electrical stimulation is more effective than nerve growth factor (NGF) infusion in inducing nerve sprouting and SCD in dogs with myocardial infarction (MI) and complete atrioventricular block (CAVB). METHODS: We gave subthreshold electrical stimulation to the left stellate ganglion (LSG) in six normal dogs for 41+-9 days (protocol 1) and to six dogs with MI and CAVB for 41+-29 days, while continuously monitoring their cardiac rhythm (protocol 2). We also monitored the rhythm of two dogs with MI, CAVB, and NGF infusion to the LSG and determined the ventricular nerve density in six healthy control dogs. RESULTS: In protocol 1, the hearts from dogs with LSG electrical stimulation had a higher density of nerve fibers immunopositive to tyrosine hydroxylase, synaptophysin, and growth-associated protein-43 than those of normal control dogs ($p<0.01$). In protocol 2, there was a high magnitude of cardiac nerve sprouting in all dogs studied. Ventricular tachycardia gtoreq8 beats and gtoreq20 beats was more frequent in dogs with electrical stimulation than in dogs with NGF infusion to the LSG (36+-60 and 11+-17 vs. 4.7+-6.1 and 0.1+-0.33 episodes per day, $p<0.05$ and $p<0.03$, respectively). Four of six dogs in protocol 2 had SCD. CONCLUSIONS: Subthreshold electrical stimulation of the LSG induces cardiac nerve sprouting and sympathetic hyperinnervation and facilitates the development of a high-yield canine model of ventricular arrhythmia and SCD.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, complete atrioventricular block, heart disease, therapy, myocardial infarction, heart disease, vascular disease, therapy, sudden cardiac death, long term subthreshold electrical stimulation, clinical techniques, therapeutic and prophylactic techniques.

Syuu, Y., H. Matsubara, T. Kiyooka, S. Hosogi, S. Mohri, J. Araki, T. Ohe, and H. Suga (2001). **Cardiovascular beneficial effects of electroacupuncture at Neiguan (PC-6) acupoint in anesthetized open-chest dog.** *Japanese Journal of Physiology* 51(2): 231-8. ISSN: 0021-521X.

NAL Call Number: QP34.5.J3

Abstract: Neiguan (PC-6) is a traditional acupoint in the bilateral forearms, overlying the median nerve trunk. Neiguan electroacupuncture (EA) has been believed to affect cardiovascular function and used in traditional Chinese medicine to improve or treat a wide range of health conditions and diseases, including angina pectoris, myocardial infarction, hypertension, and hypotension. However, few physiological studies have assessed the beneficial effects of Neiguan EA on the cardiovascular function. In the present study, we investigated its effects on the cardiovascular function in normal open-chest dogs under pentobarbital and fentanyl anesthesia. We also obtained left ventricular (LV) pressure-volume (P-V) data with a micromanometer catheter and a volumetric conductance catheter. Mean arterial pressure, end-diastolic volume, heart rate, stroke volume, cardiac output, and end-systolic pressure gradually decreased by 5 to 10% over 1.5 h without Neiguan EA. Neiguan EA at 40 Hz, however, increased these cardiovascular variables by 10 to 15%, especially end-systolic elastance (Ees) by 40% ($p<0.05$) over 15 to 60 min. After Neiguan EA was stopped at 1 h, these facilitated cardiovascular variables decreased below the pre-EA level. This beneficial effect of electroacupuncture may contribute to the effectiveness of the acupuncture in Chinese medicine.

Descriptors: animal model, Neiguan electroacupuncture, traditional acupoints, cardiovascular function, pentobarbital, fentanyl,anesthesia, left ventricular (LV) pressure-volume (P-V) data, micromanometer catheter, mean arterial pressure, end-diastolic volume, heart rate, stroke volume, cardiac output, end-systolic pressure.

Szabo, G., P. Soos, S. Mandera, U. Heger, C. Flechtenmacher, L. Seres, Z. Zsengeller, F.U. Sack, C. Szabo, and S. Hagl (2004). **Mesenteric injury after cardiopulmonary bypass: role of poly(adenosine 5'-diphosphate-ribose) polymerase.** *Critical Care Medicine* 32(12): 2392-7. ISSN: 0090-3493.

Abstract: OBJECTIVES: To investigate the effects of the ultrapotent poly(adenosine 5'-diphosphate-ribose) polymerase (PARP) inhibitor INO-1001 on cardiac and mesenteric function during reperfusion in an experimental model of cardiopulmonary bypass with cardioplegic arrest. DESIGN: Prospective, randomized, and blinded experimental study. SETTING: Research laboratory. SUBJECTS:: Twelve anesthetized dogs underwent cardiopulmonary bypass with hypothermic cardioplegic cardiac arrest. INTERVENTIONS: After 60 mins of hypothermic cardiac arrest, either PARP inhibitor INO-1001 (1 mg/kg, n = 6) or vehicle (control, n = 6) was administered during reperfusion. MEASUREMENTS AND MAIN RESULTS: Left ventricular hemodynamic variables were measured by combined pressure-volume-conductance catheters. Coronary and mesenteric blood flow and vasodilatory responses to acetylcholine and sodium nitroprusside as well as mesenteric lactate and creatinine phosphokinase release were also determined. The administration of INO-1001 led to a significantly improved recovery of left ventricular systolic function ($p < .05$) after 60 mins of reperfusion. Coronary and mesenteric blood flow were also significantly higher in the INO-1001 group ($p < .05$). Although the vasodilatory response to sodium nitroprusside

was similar in both groups before and after cardiopulmonary bypass and similar in response to acetylcholine before cardiopulmonary bypass, PARP-inhibited dogs had lower mesenteric vascular resistance after cardiopulmonary bypass ($p < .05$). Mesenteric lactate and creatinine phosphokinase release was significantly lower in the PARP inhibitor treated group ($p < .05$). CONCLUSION: PARP inhibition with INO-1001 improves the recovery of myocardial function and prevents mesenteric vascular dysfunction and tissue injury after cardiopulmonary bypass with hypothermic cardiac arrest.

Descriptors: cardiac function, mesenteric function, ultrapotent poly(adenosine 5'-diphosphate-ribose) polymerase (PARP), cardiopulmonary bypass .

Szigeti, Z., K. Simon, J.R. Parratt, and A. Vegh (2004). **Effects of delayed preconditioning on myocardial regional contractility during repeated episodes of low-flow ischaemia in anaesthetized dogs: possible role of nitric oxide.** *Clinical Science (London)* 106(2): 201-213. ISSN: 0143-5221.

NAL Call Number: RB37.C43

Abstract: The effect of cardiac pacing on repeated low-flow ischaemia-induced changes in regional myocardial segmental contractility, and the role in these changes of nitric oxide, were investigated in anaesthetized dogs. Dogs were instrumented for cardiac pacing (pacing electrode in the right ventricle). Dogs were paced (four times for 5 min; pacing rate 220 beatscntdotmin-1) 24 h prior to the repeated ischaemic insults. Controls were instrumented, but not paced. After 24 h, the dogs were re-anaesthetized with pentobarbitone and subjected to four 20 min low-flow ischaemia and reperfusion cycles, by constricting the left anterior descending coronary artery (LAD) to achieve an approx. 50% reduction in resting coronary blood flow. In some dogs (both control and paced), NG-nitro-L-arginine methyl ester (L-NAME; a non-selective inhibitor of nitric oxide synthase) was infused into a side-branch of the LAD 10 min prior to the first ischaemia/reperfusion cycle. Regional contractile function was measured by ultrasonic microcrystals in the ischaemic and normal regions of the left ventricular wall supplied from the LAD and left circumflex coronary artery respectively, and expressed as percentage changes in segmental shortening (%SS). In some dogs, myocardial tissue blood flow (coloured microspheres) and lactate production (local coronary venous sampling) were measured; samples were also taken for histological analysis. In control dogs, the regional %SS was progressively reduced within the ischaemic segment during the four repeated occlusions (by 40+-6, 59+-6, 68+-6, 70+-6% during occlusions 1-4 respectively). These reductions were more pronounced, especially during the first two cycles (68+-6, 68+-6, 67+-6, 67+-6%, respectively), when the dogs had been previously subjected to cardiac pacing. In both paced and control dogs, these changes in contractile function were L-NAME-sensitive. Thus, in the presence of L-NAME, changes in regional segmental shortening in control dogs were 37+-8, 40+-8, 37+-8, 42+-11% and in the paced dogs 4+-6, 45+-7, 45+-8, 45+-7% respectively, during the four consecutive occlusions. There were no significant differences in tissue blood flow or in lactate production between the groups, and no structural changes indicative of infarction. These results show that the myocardium rapidly adapts to re-occurring acute ischaemia by reducing contractility within the ischaemic segment and, thereby, metabolic demand. Furthermore, cardiac pacing 24 h prior to these ischaemic challenges induces a similar adaptive response, a form of 'delayed preconditioning'. Since both the acute and delayed adaptation were L-NAME-sensitive, we suggest that this

adaptation involves nitric oxide.
Descriptors: cardiovascular system, transport and circulation, histology, histology and cytology techniques, laboratory techniques.

Tabata, T., R.A. Grimm, J. Asada, Z.B. Popovic, H. Yamada, N.L. Greenberg, D.W. Wallick, Y. Zhang, S. Zhuang, K.A. Mowrey, J.D. Thomas, and T.N. Mazgalev (2004). **Determinants of lv diastolic function during atrial fibrillation: beat-to-beat analysis in acute dog experiments.** *American Journal of Physiology* 286(1 Part 2): H145-H152. ISSN: 0002-9513.
NAL Call Number: 447.8 Am3
Abstract: Left ventricular (LV) diastolic function during atrial fibrillation (AF) remains poorly understood due to the complex interaction of factors and beat-to-beat variability. The purpose of the present study was to elucidate the physiological determinants of beat-to-beat changes in LV diastolic function during AF. The RR intervals preceding a given cardiac beat were measured from the right ventricular electrogram in 12 healthy open-chest mongrel dogs during AF. Doppler echocardiography and LV pressure and volume beat-to-beat analyses were performed. The LV filling time (FT) and early diastolic mitral inflow velocity-time integral (Evti) were measured using the pulsed Doppler method. The LV end-diastolic volume (EDV), peak systolic LV pressure (LVP), minimum value of the first derivative of LV pressure curve (dP/dtmin), and the time constant of LV pressure decay (tau) were evaluated with the use of a conductance catheter for 100 consecutive cardiac cycles. Beat-to-beat analysis revealed a cascade of important causal relations. LV-FT showed a significant positive linear relationship with Evti (r=0.87). Importantly, there was a significant positive linear relationship between the RR interval and LV-EDV in the same cardiac beat (r=0.53). Consequently, there was a positive linear relationship between LV-EDV and subsequent peak systolic LVP (r=0.82). Furthermore, there were significant positive linear and negative curvilinear relationships between peak systolic LVP and dP/dtmin (r=0.95) and tau (r=-0.85), respectively, in the same cardiac beat. In addition, there was a significant negative curvilinear relationship between dP/dtmin and tau (r=-0.86). We have concluded that the determinants of LV diastolic function in individual beats during AF depend strongly on the peak systolic LVP. This suggests that the major benefit of slower ventricular rate appears related to lenthening of LV filling interval, promoting subsequent higher peak systolic LVP and greater LV relaxation.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, atrial fibrillation, heart disease, doppler echocardiography, clinical techniques, diagnostic techniques, cardiac cycle.

Takahara, A., A. Sugiyama, Y. Satoh, Y. Nakamura, T. Konda, and K. Hashimoto (2003). **L-plus n-type ca2+ channel blocker cilnidipine reduced arrhythmogenic substrates in the canine sudden cardiac death model with hypertension.** *American Journal of Hypertension* 16(5 Part 2): 130A. ISSN: 0895-7061.
NAL Call Number: RC685.H8
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology, arrhythmia, heart disease, atrio ventricular block, hypertension, vascular disease, sudden cardiac death, holter electrocardiography, laboratory techniques, cardiac output, electrophysiological parameters, hemodynamic parameters, mean blood pressure, monophasic action potential, neurohumoral parameters, ventricular repolarization.

Takahara, A., A. Sugiyama, Y. Satoh, M. Yoneyama, and K. Hashimoto (2003). **Cardiovascular effects of y-27632, a selective rho-associated kinase inhibitor, assessed in the halothane-anesthetized canine model.** *European Journal of Pharmacology* 460(1): 51-57. ISSN: 0014-2999.

NAL Call Number: QP901.E8

Abstract: Y-27632, (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, is a selective Rho-associated kinase inhibitor, which has been suggested to possess multiple clinical applications based on the in vitro observations. Since information regarding in vivo cardiovascular effects of Y-27632 is still limited, we assessed them using the halothane-anesthetized, closed-chest canine model. Administration of Y-27632 in a dose of 0.01 mg/kg, i.v. significantly decreased total peripheral vascular resistance together with an increase of cardiac output without affecting other cardiovascular parameters. Moreover, additional administration of Y-27632 in a dose of 0.1 mg/kg, i.v. significantly decreased blood pressure and left ventricular end-diastolic pressure, increased the heart rate and cardiac contractility, enhanced atrioventricular conduction and shortened the repolarization process as well as the effective refractory period. These results indicate that Y-27632 exerts a potent arterio-venodilator action with cardiostimulatory effects possibly through the sympathetic reflex in the in vivo canine model.

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, arterio venodilator action, blood pressure, cardiac contractility, cardiac output, heart rate, left ventricular end diastolic pressure, monophasic action potential, sympathetic reflex.

Takahashi, M., T. Nakamura, T. Toba, H. Kato, and Y. Shimizu (2003). **Cell transplantation of endothelial progenitor cells into lung improves pulmonary hypertension canine model.** *XXX Congress of the European Society for Artificial Organs (ESAO) on High Tech and Medicine, Aachen, Germany; September 03-06, 2003,*Vol. 26(7): 611,

Descriptors: cardiovascular system, transport and circulation, respiratory system, respiration, pulmonary hypertension, vascular disease, therapy, cell transplantation, clinical techniques, therapeutic and prophylactic techniques, neovascularization .

Takehana, K., G.A. Beller, M. Ruiz, F.D. Petruzella, D.D. Watson, and D.K. Glover (2001). **Assessment of residual coronary stenoses using 99mtc-n-noet vasodilator stress imaging to evaluate coronary flow reserve early after coronary reperfusion in a canine model of subendocardial infarction**. *Journal of Nuclear Medicine* 42(9): 1388-1394. ISSN: 0161-5505.

NAL Call Number: RM845.J78

Abstract: Reperfusion is often incomplete after recanalization therapy because of the presence of residual coronary stenoses. Detecting mild to moderate stenoses requires assessing coronary flow reserve with vasodilator stress. 99mTc-(N-ethoxy-N-ethyl-dithiocarbamato) nitrido (N-NOET) is a viability-independent flow tracer and thus may be well suited for assessing coronary flow reserve in the acute phase of reperfusion. Methods: Twelve open-chest dogs underwent 60 min of total left anterior descending artery (LAD) occlusion followed by either full reperfusion (group 1; n = 4) or reperfusion through a residual critical stenosis (group 2; n = 8). 99mTc-N-NOET was given during peak vasodilator stress 165 min after reperfusion, and initial and 60-min delayed images were acquired. Regional blood flow was

assessed with radiolabeled microspheres. Results: Infarct size was similar in both groups (9% +- 2% vs. 8% +- 2% of left ventricle). Both initial (0.61 +- 0.02 vs. 0.73 +- 0.01; P < 0.01) and 60-min (0.67 +- 0.02 vs. 0.80 +- 0.01; P < 0.01) defect count ratios (LAD/left circumflex coronary artery (LCx)) differentiated between the 2 groups, reflecting the greater diminution in coronary flow reserve in group 2 dogs (LAD/LCx flow ratios = 0.37 +- 0.04 vs. 0.57 +- 0.09; P < 0.01). Interestingly, coronary flow reserve in the reperfused zone of group 1 was diminished despite the absence of a stenosis. Thus, the difference in 99mTc-N-NOET uptake between the 2 groups was less than expected. Conclusion: In this canine myocardial infarction model with some coronary flow reserve preservation, 99mTc-N-NOET imaging can detect residual coronary stenoses. However, with more prolonged occlusion resulting in more severe endothelial or microvascular dysfunction, it may be difficult to distinguish varying degrees of vessel patency using any coronary flow reserve technique.

Descriptors: cardiovascular system, transport and circulation, pharmaceuticals, pharmacology, radiation biology, subendocardial infarction, heart disease, vascular disease, coronary flow reserve, coronary reperfusion, coronary stenosis, nuclear medicine.

Takehana, K., M. Ruiz, F.D. Petruzella, D.D. Watson, G.A. Beller, and D.K. Glover (2000). **Detection of residual coronary stenoses by assessing coronary flow reserve using 99mtc-n-noet vasodilator stress imaging early after coronary reperfusion in a canine model of infarction**. *Journal of the American College of Cardiology* 35(2 suppl. A): 493A. ISSN: 0735-1097.

NAL Call Number: RC681.A1

Descriptors: cardiovascular system, transport and circulation, myocardial infarction, heart disease, vascular disease, coronary flow reserve assessment, coronary reperfusion, residual coronary stenosis detection, vasodilator stress imaging, detection method, meeting abstract.

Tarpey, S.B., D.R. Sawmiller, C. Kelly, W.J. Thompson, and M.I. Townsley (2003). **Phosphodiesterase 3 activity is reduced in dog lung following pacing-induced heart failure.** *American Journal of Physiology* 284(5 Part 1): L766-L773. ISSN: 0002-9513.

NAL Call Number: 447.8 Am3

Abstract: We hypothesized that decreases in expression and/or activity of cAMP-specific phosphodiesterases (PDE) contribute to protective adaptations observed in lung after heart failure. In this study, we compared PDE activity in lung parenchyma isolated from control dogs and those paced to heart failure by assaying cyclic nucleotide hydrolysis in fractions of homogenate supernatant eluted from DEAE-Trisacryl columns. Cyclic nucleotide hydrolysis due to PDE3, PDE4, and PDE5 isoforms was predominant in both control and paced groups. The ratio of PDE3 activity to total cAMP PDE activity was decreased in the paced group compared with control (P<0.05), whereas PDE4 or PDE5 activity ratios were not different between the two groups. With the use of RT-PCR, message expression for PDE3A or PDE3B did not differ between the two groups. Cilostamide, a selective PDE3 inhibitor, and forskolin, a nonspecific agonist for adenylyl cyclase, both inhibited thapsigargin-induced increases in endothelial permeability in control lung. We conclude that PDE3 activity, but not mRNA expression, is reduced in lung from dogs paced to heart failure, a change that could contribute to heart failure-induced attenuation of the lung endothelial permeability response to injury.

Descriptors: cardiovascular system, transport and circulation, enzymology, biochemistry and molecular biophysics, respiratory system, respiration, heart failure, heart disease, cardiac pacing, laboratory techniques.

Thibault, B., A. Ducharme, Y.F. Shi, M. Dubuc, P. Guerra, L. Macle, D. Roy, M. Talajic, and J.C. Tardif (2004). **In the rapid pacing canine model of heart failure, left ventricular stimulation resynchronizes better the left ventricle compared to biventricular or right ventricular stimulation: an echocardiographic-hemodynamic correlation of systolic and diastolic function.** *Journal of the American College of Cardiology* 43(): (5 Supplement A): 132A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, left ventricular dysfunction, heart disease, mitral regurgitation, severe heart failure, resynchronization therapy, clinical techniques, therapeutic and prophylactic techniques, lvef [left ventricular ejection fraction], pr interval, pulmonary pressure.

Thompson, K., R.T. Thompson, J. Sykes, and G. Wisenberg (2003). **Long-term magnetic resonance imaging/spectroscopy study of cariporide in a canine cardiac ischemia/reperfusion model.** *Journal of Cardiovascular Pharmacology* 41(4): 536-543. ISSN: 0160-2446.
Abstract: Using both 31P and 1H cardiac magnetic resonance techniques, it is possible to monitor the functional (ejection fraction (EF)) and biochemical (pH) status of the heart following a reperfused ischemic insult. This study assessed the effects of Na+/H+ exchange inhibition with cariporide in a closed-chest canine ischemia/reperfusion model. Dogs received 1-mg/kg cariporide treatments for 3 days after occlusion, but were monitored for 10 days. Baseline intracellular pH (+-SEM) for the control and treated groups were 7.10 +- 0.03 and 7.14 +- 0.04, respectively, and dropped to 6.25 +- 0.08 and 6.38 +- 0.08 during occlusion. There was a significant increase in pH from occlusion to early reperfusion in the control group (P = 0.03) but, during the same time period, this increase was not seen in the cariporide group. There was a significant (P = 0.01) drug interaction in recovery of EF over the 10-day protocol. Individual time-point analysis revealed significant differences at immediate reperfusion through day 3 (73.9% +- 2.5%, 84.5% +- 3.1%; baseline normalized EF controls and cariporide, respectively). Neither pH nor EF measurements were significantly different between the groups at day 10. Despite early functional and metabolic benefits, infarct size, as measured at day 10, was 13.2% +- 2.2% for the controls and 11.8% +- 2.3% for the cariporide group (NS). Thus there were no long-term cariporide functional or biochemical benefits.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, cardiac ischemia reperfusion injury, heart disease, injury, vascular disease, magnetic resonance imaging, imaging and microscopy techniques, laboratory techniques, magnetic resonance spectroscopy, spectrum analysis techniques, ejection fraction, intracellular ph, long term study, sodium ion proton exchange.

Thomsen, M.B., P.G.A. Volders, M. Stengl, R.L. Spatjens, J.D.M. Beekman, U. Bischoff, M.A. Kall, K. Frederiksen, J. Matz, and M.A. Vos (2003). **Electrophysiological safety of sertindole in dogs with normal and remodeled hearts.** *Journal of Pharmacology and Experimental Thera-*

peutics 307(2): 776-784. ISSN: 0022-3565.
NAL Call Number: 396.8 J82
Abstract: Inhibition of the potassium current IKr and QT prolongation are associated with drug-induced torsades de pointes arrhythmias (TdP) and sudden cardiac death. We investigated the cardiac electrophysiological effects of sertindole, an antipsychotic drug reported to prolong the QT interval in schizophrenic patients. In cell cultures, sertindole seemed to be a selective blocker of IHERG over other ion currents. For IHERG, the IC50 value was 64 +- 7 nM, whereas ISCN5A, ICa,L, ICa,T, IKCNQ1/KCNE1, and IKv4.3 were blocked in the micromolar range. In canine ventricular myocytes, the IC50 value for IKr inhibition by sertindole was 107 +- 21 nM. Action potentials in these cells prolonged in a reverse rate- and concentration-dependent manner at 10 to 300 nM sertindole. In vivo, sertindole was administered to anesthetized dogs at clinically relevant (0.05-0.20 mg/kg) and high doses (1.0-2.0 mg/kg) i.v. At 0.05 to 0.20 mg/kg sertindole (plasma concentrations 30-157 nM), QTc was prolonged by 1 to 5% in normal dogs and by 9 to 20% in dogs with remodeled hearts due to chronic atrioventricular block (CAVB). TdP was not induced at these doses in normal dogs or in CAVB dogs with reproducible induction of TdP by dofetilide in previous experiments. At 1.0 to 2.0 mg/kg sertindole (plasma concentrations 0.5-3.1 muM), QTc prolonged by 6 to 11% in normal dogs and by 22% in dofetilide-sensitive CAVB dogs. TdP occurred in three of five animals in the latter group. Thus, at high i.v. doses sertindole can pose a serious proarrhythmic risk when electrical remodeling of the ventricles is present. At clinically relevant doses, however, sertindole does not cause TdP in anesthetized dogs with normal or remodeled hearts.
Descriptors: behavior, cardiovascular system, transport and circulation, pharmacology, schizophrenia, behavioral and mental disorders, drug therapy, sudden cardiac death, heart disease, toxicity, drug induced, prevention and control, torsades de pointes arrhythmias, drug induced, prevention and control, electrophysiology, clinical techniques, i ca,l current, i ca,t current, i herg current, i kcnq1, kcne1 current, i kv4.3 current, i scn5a current, qt prolongation, chronic atrioventricular block.

Thornhill, R.E., F.S. Prato, G. Wisenberg, G.R. Moran, and J. Sykes (2004). **Determining the extent to which delayed-enhancement images reflect the partition-coefficient of gd-dtpa in canine studies of reperfused and unreperfused myocardial infarction**. *Magnetic Resonance in Medicine* 52(5): 1069-1079. ISSN: 0740-3194.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, myocardial infarction, heart disease, vascular disease, prevention and control, therapy, bolus, drug delivery device, delayed enhancement imaging, imaging and microscopy techniques, laboratory techniques, infusion therapy, clinical techniques, therapeutic and prophylactic techniques, magnetic resonance imaging, clinical techniques, diagnostic techniques, image delay time, necrosis, partition coefficient, time postinfarction.

Tonduangu, D., L. Hittinger, B. Ghaleh, P. Le Corvoisier, L. Sambin, S. Champagne, T. Badoual, F. Vincent, A. Berdeaux, B. Crozatier, and J.B. Su (2004). **Chronic infusion of bradykinin delays the progression of heart failure and preserves vascular endothelium-mediated vasodilation in conscious dogs.** *Circulation* 109(1): 114-119. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8

Abstract: Background-This study examined the effects of chronic bradykinin infusion on hemodynamics and myocardial and endothelial functions during the development of heart failure. Methods and Results-Sixteen instrumented dogs were randomized to receive through the left atria either vehicle or bradykinin (1 mug/min) during ventricular pacing (250 bpm, 5 weeks). Hemodynamic and left ventricular (LV) parameters and the vasodilator responses to intravenous acetylcholine (0.3 to 3 mug/kg) and nitroglycerin (1 to 10 mug/kg) were examined in the control and after 3 and 5 weeks of pacing. The expression of endothelial NOS in femoral, carotid, and renal arteries was determined by Western blot analysis. After 3 weeks of pacing, changes in LV diastolic and systolic parameters were significantly lower in bradykinin-treated than vehicle-treated dogs (LV end-diastolic pressure, +10+-3 versus +19+-2 mm Hg; time constant of LV isovolumic relaxation, +11+-2 versus +17+-1 ms; LV wall thickening, -33+-18% versus -75+-9%; and cardiac output, -16+-6% versus -32+-6%; all P<0.05). Compared with vehicle-treated dogs, bradykinin-treated dogs had a reduced rightward shift of the diastolic LV pressure-diameter relation and a reduced diastolic LV wall stress. Similar trends were observed after 5 weeks. The vasodilator response to nitroglycerin was preserved in both groups. The response to acetylcholine was blunted in vehicle-treated but preserved in bradykinin-treated dogs. Vascular endothelial NOS expression decreased in vehicle-treated but was preserved in bradykinin-treated dogs. Conclusions-In conscious dogs, chronic bradykinin infusion delays the heart failure progression by preserving LV diastolic and systolic functions and by preserving vascular endothelial function.
Descriptors: cardiovascular system, transport and circulation, pharmacology, heart failure, heart disease, hemodynamics, myocardial functions, vascular endothelium mediated vasodilation.

Trumble, D.R. and J.A. Magovern (2004). **Comparison of dog and pig models for testing substernal cardiac compression devices.** *ASAIO Journal (American Society for Artificial Internal Organs)* 50(3): 188-92. ISSN: 1058-2916.

Abstract: Subtle anatomic differences between species can be a critical consideration when determining whether a given animal model is appropriate for surgical research purposes, especially when testing biomechanical implants. This study compares the effectiveness of two common animal models (dogs and pigs) in testing a balloon based cardiac compression device designed for substernal placement. Pigs were used in acute studies using an infarction model of heart failure, whereas dogs were used in chronic experiments in which heart failure was induced via rapid pacing. Systolic cardiac compression was accomplished in both species using identical balloons inflated between the sternum and right ventricle with every heartbeat. Results showed the device to be much more effective in pigs, where cardiac stroke volumes returned to normal with balloon assistance (14.7 +/- 1.9 to 37.8 +/- 9.2 mL, p < 0.005). Stroke volumes in dogs, however, remained essentially unaltered by balloon activation (28.1 +/- 14.1 to 29.6 +/- 14.7 mL, p = NS). Retrospective comparisons showed pig models to be a much closer approximation to the human anatomy because of a more similar thoracic cavity shape and heart orientation. These findings suggest that certain large animal models should not be used in research in which chest wall shape or cardiac orientation within the thoracic cavity may influence outcomes.
Descriptors: animal model, species differences, dog versus pig, antomical differences, surgical research, biomechanical implants, infarction models, heart failure.

Tse, L.W., B.T. Bui, S. Lerouge, I. Salazkin, E. Therasse, A. Benko, H. Heon, V.L. Oliva, and G. Soulez (2007). **In vivo antegrade fenestration of abdominal aortic stent-grafts.** *Journal of Endovascular Therapy an Official Journal of the International Society of Endovascular Specialists* 14(2): 158-67. ISSN: 1526-6028.

Abstract: PURPOSE: To examine in a canine model the feasibility of antegrade fenestration of abdominal aortic stent-grafts to preserve the patency of the renal arteries. METHODS: Two large dogs underwent antegrade fenestration of stent-grafts in the perirenal aorta. Before fenestration, bare stents were inserted in both renal arteries as fluoroscopic landmarks. A 12-mm iliac extension served as the canine aortic endograft. The first procedure was done under ultrasound and fluoroscopic guidance, using an intravascular ultrasound (IVUS) probe inserted in the vena cava and a Pioneer IVUS catheter. The second was performed exclusively under fluoroscopic guidance with a Brockenbrough needle. Angiograms and duplex ultrasound were planned for 1 month, after which the dogs would be sacrificed for autopsy. The explanted endograft was subjected to biomaterials analysis, with a focus on fabric tear. RESULTS: Perforation of the aortic graft and catheterization of the renal arteries with a floppy guidewire were possible in both animals. In dog 1, aortic graft dilation and subsequent fenestration were not possible, and the experiment was terminated. However, the procedure was successful in both renal arteries of dog 2. At 1-month follow-up in this dog, both renal arteries were patent. Stent fractures were observed bilaterally. There was no extension of the damage to the fabric beyond the area of fenestration. CONCLUSION: In vivo antegrade fenestration of aortic endografts is technically feasible. However, improvements in technique, instrumentation, and materials are required to make it a reliable and reproducible way of allowing stent-graft vascularization of aortic side branches.

Descriptors: aorta, abdominal surgery, blood vessel prosthesis, blood vessel prosthesis implantation, renal artery surgery, stents, aorta, abdominal radiography, aorta, abdominal ultrasonography, aortography, dogs, feasibility studies, models, animal, prosthesis design, radiography, interventional, renal artery radiography, renal artery ultrasonography, time factors, ultrasonography, interventional, vascular patency.

Tsutsui, J.M., P.M. Dourado, A.C.P. Chagas, W.J. Mathias, J.L. Andrade, and P.L. Da Luz (2003). **Evaluation of infarcted and risk areas by real-time myocardial contrast echocardiography in an open-chest canine model.** *FASEB Journal* 17(4-5): Abstract No. 342.17. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: cardiovascular system, transport and circulation, methods and techniques, ischemia, vascular disease, myocardial infarction, heart disease, real time myocardial contrast echocardiography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, infarcted, risk areas, evaluation method, methodology, open chest canine model, uses, perfusional myocardial defects, evaluation, wall motion defects, evaluation.

Tucci, P.J.F., O.J. Sant'ana, R.J. Nogueira, N. Murad, A.C. Lopes, A. Sanudo, and C.A. Peres (2003). **Stunning and myocardial contractile autoregulation studied on the isolated isovolumic blood-perfused dog heart.** *Acta Physiologica Scandinavica* 179(3): 263-271. ISSN: 0001-6772.

NAL Call Number: QP1.A2
Abstract: Aim: To study, for the first time, the effects of stunning on homeometric and heterometric autoregulation. Methods and results: Ischaemia (15 min)/reperfusion (30 min) was induced in the isovolumic blood-perfused dog heart preparation. Heart rate elevations (n = 9) from 60 to 200 beats min-1, in steps of 20 beats min-1, promoted the same inotropic stimulation in control (C) and stunning (S), indicating that ischaemia/reperfusion does not affect the changes in calcium kinetics elicited by the Bowditch effect. Sudden ventricular dilation (VD) (n = 10) evoked an instantaneous increase in developed pressure (DELTA1DP) followed by a continuous slow performance increase (DELTA2DP) in C and S. DELTA1DP (C:35 +- 2.2 mmHg; S:27 +- 2.1 mmHg; P = 0.002) and DELTA2DP (C:20 +- 1.6 mmHg; S:14 +- 1.3 mmHg; P = 0.002) decreased proportionally, while DELTA2DELTADP (C:0.57 +- 0.13; S:0.58 +- 0.14) and slow response time course (T/2) were unchanged (C:55 +- 6.6 s; S:57 +- 7.7 s) after ischaemia/reperfusion. The reduction of DELTA1DP can be understood as a decline of the myofilaments calcium responsiveness, the main pathophysiological effect of stunning. The reason for the weakening of DELTA2DP, due to intracellular calcium gain, was not determined but it was supposed that its complete manifestation could be restricted by cyclic adenosine monophosphate (cAMP) myocardial content reduction. As reported by others, DELTA2DP depends on myocardial cAMP, and it has been shown that myocardial cAMP is decreased after ischaemia/reperfusion. Conclusions: Contractile depression due to stunning has no effect on the inotropic stimulation generated by the Bowditch phenomenon. Immediate and time-dependent enhancements of contraction evoked by sudden VD are proportionally reduced and the slow response time course is unaffected in the stunned myocardium.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, methods and techniques, ischemia,vascular disease, myocardial stunning, heart disease, vascular disease, heart rate.

van Opstal, J.M., P.G. Volders, M. Stengl, E. Martel, U. Gerlach, R.L. Spatjens, J.D. Beekman, K.R. Sipido, and M.A. Vos (2003). **Iks contributes importantly to ventricular repolarization in conscious dogs.** *Journal of the American College of Cardiology* 41(6 Supplement A): 112A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation.

Vanderheide, R.S. (2000). **Overexpression of stress proteins protects cultured adult canine ventricular myocytes from simulated ischemia/reperfusion injury**. *Circulation* 102(18 Supplement): II.272. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, adenovirus infection, viral disease, cardiac heat shock protein expression, myocardial ischemic injury, heart disease, development, mediation, cell death, meeting abstract.

Verdonck, F., P.G.A. Volders, M.A. Vos, and K.R. Sipido (2003). **Increased na+ concentration and altered na/k pump activity in hypertrophied canine ventricular cells.** *Cardiovascular Research* 57(4): 1035-1043. ISSN: 0008-6363.

NAL Call Number: QM178.A1C38
Abstract: Objective: To investigate whether hypertrophy in the dog with chronic atrioventricular block (CAVB) alters (Na+)i and Na/K-pump function of ventricular myocytes. Methods: We measured the (Na+)i dependence of the Na/K pump current, Ip. This relation was used as a calibration curve for (Na+)i based on Ip. We measured Ip at the time of access and extrapolated (Na+) at the pump sites, i.e. subsarcolemmal (Na+), (Na+)subs, from the calibration curve. Results: The extrapolated (Na+)subs was significantly higher in CAVB (7.9 vs. 3.2 mM in control). The (Na+)i dependence of Ip in CAVB myocytes was shifted to the right (range of (Na+)i: 0-20 mM). In resting cells, the Ip, i.e. steady state Na+ efflux, which matches Na+ influx, was higher in CAVB (0.25+-0.02 vs. 0.47+-0.06 pA/pF, P<0.05). Maximal Ip density was not different, and DHO sensitivity was not altered. Conclusions: Hypertrophy in CAVB cells is associated with increased (Na+)subs. This results from an increase in Na+ influx, and a decreased sensitivity of Ip for Na+ in the range of (Na+)i studied. There is no evidence for a decrease in total pump capacity or for a functional Na/K-ATPase isoform shift. The rise in Na+ contributes to the contractile adaptation and preservation of sarcoplasmic reticulum Ca2+ content at the low heart rates of the dog with CAVB.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, cell biology, metabolism, cardiac hypertrophy, heart disease, chronic atrioventricular block.

Veres, G., T. Radovits, H. Schultz, L.N. Lin, J. Hutter, E. Weigang, Z. Szabolcs, and G. Szabo (2007). **Effect of recombinant aprotinin on postoperative blood loss and coronary vascular function in a canine model of cardiopulmonary bypass.** *European Journal of Cardio Thoracic Surgery Official Journal of the European Association for Cardio Thoracic Surgery* 32(2): 340-5. ISSN: 1010-7940.
NAL Call Number: RD598
Abstract: OBJECTIVE: Aprotinin is a widely used serine protease inhibitor during cardiopulmonary bypass to reduce blood loss and preserve platelet function. However, the bovine-derived aprotinin can induce hypersensitivity reaction with fatal complications. Furthermore, vascular effects of aprotinin are not completely elucidated. The current study is designed to investigate the effects of recently developed recombinant aprotinin on blood loss and coronary vascular function in a clinically relevant canine model of cardiopulmonary bypass without aortic cross-clamping and cardioplegia. METHODS: Twenty-four dogs underwent cardiopulmonary bypass without aortic cross-clamping and cardioplegia. Dogs were divided into three groups in a blinded fashion: control animals (n=8) received placebo, aprotinin treatment groups received bovine (n=8) or recombinant aprotinin (n=8) according to the Hammersmith method. The doses of bovine and recombinant aprotinin were the same. Coagulation parameters and blood loss were measured regularly at different time points. Endothelium-dependent and -independent vasorelaxation were investigated in isolated left anterior descendent coronary arterial rings by using acetylcholine and bradykinin or sodium nitroprusside and adenosine, respectively. RESULTS: Postoperative blood loss was significantly reduced in the aprotinin-treated groups in comparison to control and there was no significant difference between the two aprotinin-treated groups. Endothelium-dependent relaxation of coronary arteries to acetylcholine and bradykinin was unaffected in

the aprotinin treatment groups. Both types of aprotinin significantly increased vasorelaxation to adenosine when compared with controls, but did not affect that to sodium nitroprusside. CONCLUSIONS: The effectiveness of recombinant aprotinin on blood loss was equivalent to bovine-derived aprotinin. Neither types of aprotinin impaired endothelium-dependent relaxation in a canine model of cardiopulmonary bypass.

Descriptors: aprotinin administration and dosage, cardiopulmonary bypass methods, coronary vessels drug effects, postoperative hemorrhage prevention and control, serine proteinase inhibitors administration and dosage, 15 hydroxy 11 alpha,9 alpha epoxymethanoprosta 5,13 dienoic acid pharmacology, acetylcholine pharmacology, blood coagulation drug effects, blood coagulation physiology, bradykinin pharmacology, cattle, coronary vessels physiopathology, dogs, drug administration schedule, endothelium, vascular drug effects, endothelium, vascular physiopathology, models, animal, myocardial contraction drug effects, myocardial contraction physiology, nitroprusside pharmacology, recombinant proteins administration and dosage, vasoconstrictor agents pharmacology, vasodilator agents pharmacology.

Verheule, S., E. Wilson, T.I. Everett, S. Shanbhag, C. Golden, and J. Olgin (2003). **Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation.** *Circulation* 107(20): 2615-2622. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8

Abstract: Background-Clinically, chronic atrial dilatation is associated with an increased incidence of atrial fibrillation (AF), but the underlying mechanism is not clear. We have investigated atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation (MR). Methods and Results-Thirteen control and 19 MR dogs (1 month after partial mitral valve avulsion) were studied. Dogs in the MR group were monitored using echocardiography and Holter recording. In open-chest follow-up experiments, electrode arrays were placed on the atria to investigate conduction patterns, effective refractory periods, and inducibility of AF. Alterations in tissue structure and ultrastructure were assessed in atrial tissue samples. At follow-up, left atrial length in MR dogs was 4.09+-0.45 cm, compared with 3.25+-0.28 at baseline (P<0.01), corresponding to a volume of 205+-61% of baseline. At follow-up, no differences in atrial conduction pattern and conduction velocities were noted between control and MR dogs. Effective refractory periods were increased homogeneously throughout the left and right atrium. Sustained AF (>1 hour) was inducible in 10 of 19 MR dogs and none of 13 control dogs (P<0.01). In the dilated MR left atrium, areas of increased interstitial fibrosis and chronic inflammation were accompanied by increased glycogen ultrastructurally. Conclusions-Chronic atrial dilatation in the absence of overt heart failure leads to an increased vulnerability to AF that is not based on a decrease in wavelength.

Descriptors: cardiovascular system, transport and circulation, atrial fibrillation, heart disease, chronic atrial dilatation, chronic inflammation, immune system disease, heart failure, interstitial fibrosis, disease miscellaneous, mitral regurgitation, holter recording, laboratory techniques, echocardiography, electrode array, laboratory equipment, partial mitral valve avulsion, experimental surgical techniques.

Vincent, I.C. and R.A. Leahy (1997). **Real-time non-invasive measurement of heart rate in working dogs: a technique with potential applications in the objective assessment of welfare problems**. *Veterinary Journal* 153(2): 179-183. ISSN: 1090-0233.
NAL Call Number: SF601.V484
Abstract: The Polar Sport Tester (Polar Electro OY) is a telemetric heart rate monitor designed for use in humans. Its usefulness as a monitor during training of guide dogs is assessed in this paper. Heart rates from six representative dogs at a similar stage of early training were recorded at 5-s intervals during a 15-20 min work session. The dogs were F1 Labrador Retriever times Golden Retrievers. They were chosen if their behaviour could be clearly categorized by their experienced trainers as either 'calm/non-stress prone' (Type A) or 'excitable/stress prone' (Type B) during work. Verbal recordings were made of environmental cues and behavioural responses in each dog. Variability in heart rate was significantly related to a subject's described temperament.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, veterinary medicine, medical sciences, breed f1 labrador x golden retriever, cardiovascular system, heart rate monitor, heart rate real time non invasive measurement, methodology, polar sport tester, potential applications, technique, temperament relation, verbal recordings, veterinary medicine, welfare problems, working dogs.

Wang, L., D.M. Zhu, X. Su, C.X. Bai, L.B. Ware, and M.A. Matthay (2004). **Acute cardiopulmonary effects of a dual-endothelin receptor antagonist on oleic acid-induced pulmonary arterial hypertension in dogs.** *Experimental Lung Research* 30(1): 31-42. ISSN: 0190-2148.
Abstract: The objective of this study was to evaluate the cardiopulmonary effects of a dual-endothelin (ET) receptor antagonist, Tezosentan, on oleic acid (OA)-induced acute lung injury with pulmonary arterial hypertension in dogs. Twelve Pentobarbital-anesthetized dogs with intravenous OA-induced acute lung injury (ALI) were divided into 2 groups. The control group (n=6) received saline treatment, whereas the treatment group (n=6) received the ET receptor antagonist, Tezosentan (1 mg/kg intravenous (IV)+1 mg/kg/h IV infusion). Cardiopulmonary parameters were monitored continuously for 1 hour. OA administration resulted in a significant increase in mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR) and a decrease in mean systemic arterial pressure (MSAP), systemic vascular resistance (SVR), and cardiac output (CO) in all-dogs. Tezosentan treatment markedly attenuated the pulmonary hypertension, with a 32% decrease in MPAP (from 23+-2 mm Hg to 15+-2 mm Hg; P<.01) and a 22% decrease in PVR (from 860+-105 dyncntdotscntdotcm-5 to 670+-96 dyncntdotscntdotcm-5; P<.01) at the end of study. MSAP and SVR were unchanged after Tezosentan treatment, and there was an increase in cardiac output and a decline in peak inspiratory pressure (PIP) in the Tezosentan group compared with the control group. These results indicate that the dual-ET receptor antagonist, Tezosentan, can attenuate the pulmonary hypertension induced by OA. Thus, dual-ET receptor antagonists such as Tezosentan may be useful in the management of acute pulmonary arterial hypertension, complicating the course of OA-induced lung injury.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, veterinary medicine, medical sciences, acute lung injury, injury, respiratory system disease, pulmonary arterial hypertension, respiratory system disease, vascular

disease, chemically induced, vascular disease, mean pulmonary arterial pressure [mpap], systemic vascular resistance.

Wang, M. and M.A. Lung (2003). **Adrenergic mechanisms in canine nasal venous systems.** *British Journal of Pharmacology* 138(1): 145-155. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: 1 We investigated the adrenergic mechanisms of the two venous systems that drain the nasal mucosa, thereby their exact role in eliciting nasal decongestion. The action of endogenously released noradrenaline and exogenous adrenergic agonists on different segments of the nasal venous systems, i.e. collecting (LCV, SCV) and outflow (SPV) veins of posterior venous system, collecting (ACV) and outflow (DNV) veins of anterior venous system and venous sinusoids of the septal mucosa (SM), were studied. In vitro isometric tension of the vascular segments was measured. 2 Transmural nerve stimulation (TNS) produced constriction in ACV, DNV and SM, primary constriction followed by secondary dilatation in LCV and SCV and dilatation in SPV. Tetrodotoxin (10-6 M) abolished all responses. Phentolamine (10-6 M), prazosin (10-6 M) and rauwolscine (10-7 M) inhibited the constriction in all venous vessels. Propranolol (10-6 M), atenolol (10-6 M) and ICI 118,551 (10-6 M) inhibited the relaxation in SPV but not in LCV and SCV. Phenylephrine and clonidine constricted whereas dobutamine and terbutaline relaxed all venous vessels dose-dependently. 3 These results indicate alpha1-, alpha2-, beta1- and beta2-adrenoceptors are present in both venous systems. TNS causes constriction of anterior venous system, venous sinusoids and posterior collecting veins primarily via postjunctional alpha2-adrenoceptors but relaxation of posterior outflow vein equally via postjunctional beta1- and beta2-adrenoceptors. The combined action of the two adrenergic mechanisms can reduce nasal airway resistance in vivo by decreasing vascular capacitance and enhancing venous drainage via the posterior venous system.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, nasal decongestion, respiratory system disease, transmural nerve stimulation, laboratory techniques, adrenergic mechanisms, isometric tension, nasal airway resistance, vascular capacitance, vasoconstriction, vasodilation, venous drainage.

Wang Qiu Jing , Lu Weng Wei , Lu Hang , Liu Fen , Yang Shi Jie , Hua Yu Qiang , and Ji Shu Xia (2003). **Protective effect of qi dong yi xin on acute myocardial infarction in dogs.** *Zhongguo Zhongyao Zazhi* 28(5): 449-452. ISSN: 1001-5302.
Abstract: Objective: To observe the protective effects on acute myocardial infarction of QDYX in dog. Method: The corconary ciculation and cardial oxygen metabolism, the degree and range of myocardial ischemia, myocardial infarct size, and the changes of the enzymes in serum were determined by using the acute myocardial infarction model of ligation of LAD in the anaesthetized open-chest dogs. Result: The coronary resistance and cardial oxygen consumption were decreased and the myocardial blood flow was increased in dogs treated with QDYX of 1.0, 2.0 mgcntdotkg-1. The degree and range of myocardial ischemia, myocardial infarct size and the activity of serum CK, LDH were decreased in acute myocardial infarcion dogs treated with QDYX of 1.0, 2.0 mgcntdotkg-1. Conclusion: QDYX can decrease cardial oxygen consumption in dogs, thus having protective effect on myocardial ischemia.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and

circulation, pharmacognosy, pharmacology, acute myocardial infarction, heart disease, vascular disease, diagnosis, prevention and control, therapy, coronary circulation.
Language of Text: Chinese.

Wang, T.M., C.E. Chiang, J.R. Sheu, C.H. Tsou, H.M. Chang, and H.N. Luk (2003). **Homogenous distribution of fast response action potentials in canine pulmonary vein sleeves: a contradictory report.** *International Journal of Cardiology* 89(2-3): 187-195. ISSN: 0167-5273.
Abstract: Pulmonary veins may serve as source of ectopic focus (or foci) in initiating atrial tachyarrhythmias in human beings. However, the animal model for such focal atrial fibrillation is still lacking and cellular mechanism for arrhythmias remains to be studied. Recently, a series of reports of cellular electrophysiological characterization of pulmonary vein sleeves demonstrated an extremely high incidence of automaticity (varied from 40 to 76%) and triggered activity (from 0 to 44%) in normal healthy control dogs and rabbits. The present study was therefore designed to re-investigate the cellular electrophysiological properties of canine pulmonary veins. Intracellular action potentials were characterized in pulmonary vein sleeves in 50 normal healthy dogs. Conventional glass microelectrode recording technique was used. Experiments were focused on the incidence of automaticity and triggered activity in pulmonary vein sleeve tissues. Surprisingly, our results showed that all pulmonary vein sleeves tissues in these dogs displayed fast-response action potentials under the well-controlled experimental condition (100%, n=50). No spontaneous pacemaking activities, early or delayed afterdepolarisations were observed (0%, n=50). No high-frequency spikes or irregular rhythm could be recorded in all experiments (0%, n=50). Both the frequency response and membrane responsiveness of the pulmonary vein action potentials were characterized. No electrophysiological inhomogeneity between the distal and the proximal part of the sleeves was observed. In conclusion, canine pulmonary vein sleeves do not display arrhythmogenic activities under normal physiological conditions. The possible explanations for the controversy in pulmonary veins electrophysiology were discussed.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, arrhythmia, heart disease, atrial fibrillation.

Weber, T.P., M.A.G. Hartlage, N. Rolf, M. Booke, E. Berendes, H. Van Aken, and A. Meissner (2003). **Short-term administration of ethanol does not affect functional recovery from myocardial stunning in awake dogs.** *Anesthesia and Analgesia* 96(3): 665-672. ISSN: 0003-2999.
Abstract: Chronic ingestion of small doses of ethanol protects the myocardium from ischemic damage. It was demonstrated that short-term administration of ethanol (SAE) enhances the recovery of stunned myocardium in acutely instrumented, anesthetized dogs. It is unclear whether this beneficial effect of SAE also occurs in awake dogs. Therefore, we investigated the effects of SAE on regional myocardial stunning in awake dogs. Thirty-six dogs were chronically instrumented for measurement of heart rate, left atrial, aortic, and left ventricular pressure, left systolic ventricular contactility (dP/dtmax) and diastolic ventricular function (dP/dtmin), and regional myocardial wall-thickening fraction (WTF). Occluders around the left anterior descending (LAD) artery allowed the induction of reversible ischemia in the LAD-perfused myocardium. The dogs were assigned to one of three groups that differed in the dose of ethanol administered in the ethanol experiment (I, 0.125 g/kg (n = 12); II,

0.25 g/kg (n = 12); III, 0.5 g/kg (n = 12)). In each group, the dogs underwent two ischemic episodes (randomized crossover fashion; separate days): 10 min of LAD occlusion after the application of ethanol IV over 30 min (ethanol group) and without ethanol (control). WTF and hemodynamic variables were measured at baseline and at predetermined time points until complete recovery of myocardial stunning occurred. LAD-ischemia led to a significant decrease of LAD-WTF in all groups. There was no difference in WTF and hemodynamic variables with or without SAE during reperfusion. We conclude that SAE (0.125 g/kg, 0.25 g/kg, and 0.5 g/kg) does not significantly affect myocardial stunning in conscious dogs.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, methods and techniques, myocardial stunning, heart disease, vascular disease.

Weinberg, G., R. Ripper, D.L. Feinstein, and W. Hoffman (2003). **Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity.** *Regional Anesthesia and Pain Medicine* 28(3): 198-202. ISSN: 1098-7339.
Abstract: Background and Objectives: We previously demonstrated in rats that intravenous infusion of a lipid emulsion increases survival in resuscitation from severe bupivacaine cardiac toxicity. The present studies were undertaken to determine if this method is similarly effective in a non-rodent model using a larger animal. Methods: Bupivacaine, 10 mg/kg, was administered intravenously over 10 seconds to fasted dogs under isoflurane general anesthesia. Resuscitation included 10 minutes of internal cardiac massage followed with either saline or 20% lipid infusion, administered as a 4-mL/kg bolus followed by continuous infusion at 0.5 mL/kg/min for 10 minutes. Electrocardiogram (EKG), arterial blood pressure (BP), and myocardial pH (pHm) and pO2 (pmO2) were continuously measured. Results: Survival after 10 minutes of unsuccessful cardiac massage was successful for all lipid-treated dogs (n=6), but with no survivors in the saline controls (n=6) (P<.01). Hemodynamics, PmO2, and pHm were improved during resuscitation with lipid compared with saline treatment in which dogs did not recover. Conclusions: We found that infusing a lipid emulsion during resuscitation from bupivacaine-induced cardiac toxicity substantially improved hemodynamics, pmO2, and pHm and increased survival in dogs.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, toxicology, resuscitation, clinical techniques, therapeutic and prophylactic techniques.

Werner, P., M.G. Raducha, U. Prociuk, E.O. Ostrander, R.S. Spielman, E.F. Kirkness, D.F. Patterson, and P.S. Henthorn (2003). **Genome-wide scan for conotruncal heart defect loci in a canine model.** *American Journal of Human Genetics* 73(5): 517. ISSN: 0002-9297.
NAL Call Number: QH431.A1A54
Descriptors: cardiovascular system, transport and circulation, molecular genetics, biochemistry and molecular biophysics, conal ventricular septal defect, congenital disease, heart disease, genetics, conotruncal heart defect, conus septum defect, isolated congenital heart defects, persistent truncus arteriosus, tetralogy of Fallot, genehunter, computer software, genehunter twolocus analysis, genetic techniques, laboratory techniques, mathematical and computer techniques, lod score, genome wide scan, two point linkage analysis, genetic techniques, autosomal recessive inheritance model, non mendelian inheritance patterns.

Willigers, H.M., F.W. Prinzen, P.M. Roekaerts, S. De Lange, and M.E. Durieux (2003). **Dexmedetomidine decreases perioperative myocardial lactate release in dogs.** *Anesthesia and Analgesia* 96(3): 657-664. ISSN: 0003-2999.

Abstract: The sympatholytic effect of the alpha2-adrenergic agonist dexmedetomidine may decrease emergence-related myocardial ischemic load in patients. However, a direct measure of myocardial ischemia, such as myocardial lactate release, is difficult to obtain in patients. Therefore, we studied mongrel dogs and measured myocardial lactate release, myocardial oxygen supply, hemodynamic variables, and neurohumoral indices of the stress response. After the induction of a standardized degree of borderline myocardial ischemia, either dexmedetomidine (dexmed group, n = 9) or normal saline (control group, n = 9) was infused. Measurements were repeated at the end of the anesthetic period and every 10 min during the 90-min emergence period. In the dexmed group, the cumulative emergence-related lactate release was 46% less than in the control group (95% confidence interval, 20%-80%; P = 0.02). Simultaneously, dexmedetomidine increased the endo-/epicardial blood flow ratio by 35% (control group, 0.4 +- 0.1; dexmed group, 0.6 +- 0.1; P = 0.03). These antiischemic effects of dexmedetomidine were accompanied by reduced plasma concentrations of norepinephrine (126 versus 577 pg/mL) and epinephrine (158 versus 1909 pg/mL) and a slower heart rate (123 +- 6 versus 160 +- 10 bpm, dexmed versus control). The antiischemic effect of dexmedetomidine started before emergence, as evidenced by a decreased prevalence of myocardial lactate release at that time (zero of eight dogs in the dexmed group and four of seven dogs in the control group had lactate release before emergence; P = 0.03).

Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, myocardial ischemia, heart disease, vascular disease.

Wu, M.H.D., Y. Kouchi, Y. Onuki, Q. Shi, H. Yoshida, S. Kaplan, R.F. Viggers, R. Ghali, and L.R. Sauvage (1995). **Effect of differential shear stress on platelet aggregation, surface thrombosis, and endothelialization of bilateral carotid-femoral grafts in the dog**. *Journal of Vascular Surgery* 22(4): 382-392. ISSN: 0741-5214.

Abstract: Purpose: The purpose of this study was to determine the effects of increased shear stress on the aggregability of platelets as they traverse a long, small-caliber (6 min) Dacron graft in the dog and on the surface thrombosis and endothelialization of such a graft. Methods: Each of nine dogs received bilateral carotid-femoral artery grafts, approximately 75 cm long, for 3 months; one graft of each pair had a distal femoral arteriovenous fistula to produce a higher shear rate than the contralateral graft. Platelet aggregation scores were determined on blood withdrawn from the external jugular vein and eta-m the proximal and distal ends of the grafts in each animal. Graft flow rates, which were used in the computation of shear stress, and luminal pressure gradients through grafts were measured during surgery and specimen retrieval. Specimens were studied with light microscopy after hematoxylin and eosin and immunocytochemical staining and by scanning electron and transmission electron microscopy to evaluate the nature, composition, and thickness of the flow surface lining, as well as the transmural healing. Results: Two high-shear stress and two low-shear stress grafts occluded unilaterally; five dogs had bilaterally patent grafts, allowing comparative analyses. AR subjects had low platelet aggregability with aspirin. Platelet aggregation scores taken from proximal and distal ends of the grafts were not significantly different. The high-shear stress grafts had significantly more endothelial-like cell coverage (p lt 0.0371) than

the low-shear stress grafts, less flow-surface thrombus (p lt 0.0056), and a thinner surface lining (p lt 0.0029), on both the neointima and pseudointima. Conclusions: In subjects with low platelet aggregation scores, long Dacron grafts do not elevate platelet aggregability of blood flowing through them. High-shear stress grafts have less flow surface thrombus, more endothelialization, and a thinner surface lining than do low-shear stress grafts.
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, cell biology, methods and techniques, morphology, physiology, axillofemoral bypass, dacron graft, graft patency, intimal hyperplasia, surgical method.

Wu, X., C.F. Wang, J. Sheng, and J. Zhu (2004). **[Changes in tissue plasminogen activator and plasminogen activator inhibitor during administration of nitroglycerine into internal thoracic artery in dogs with acute myocardial ischemia]**. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue [Chinese Critical Care Medicine]* 16(9): 527-9. ISSN: 1003-0603.
Abstract: OBJECTIVE: To study the changes in tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI) in a model of acute myocardial infarction reproduced in the dog with administration of nitroglycerin into internal thoracic artery under pressure. METHODS: Sixty healthy cross-breed dogs were randomly divided into experimental and control group with 30 dogs in each group. The animal model of acute myocardial ischemia was reproduced by ligating the left anterior descending coronary artery. Internal thoracic artery in the experimental group was ligated, and a tube was introduced into the proximal end. Nitroglycerine was infused under pressure into the internal thoracic artery in experimental group. The drug was given intravenously in control group. t-PA and PAI were measured before anterior coronary artery ligation and at 0.5, 2 and 6 hours after coronary artery ligation. RESULTS: The t-PA levels in two groups were increased at 0.5 hour after coronary artery ligation, and gradually declined in control group, while no obvious change was found in experimental group. There was significant difference between experimental group and control group at 6 hours after coronary artery ligation($P<0.05$). PAI levels were increased after coronary artery ligation, peaking at 6 and 2 hours after coronary artery ligation in both groups. Significant difference in PAI level was observed between two groups at 6 hours after coronary artery ligation($P<0.05$). CONCLUSION: Introduction of nitroglycerine through internal thoracic artery under pressure is effective to accelerate release of t-PA from the endothelium while inhibit secretion of PAI, therefore it is useful to modulate the balance of fibrinolysis.
Descriptors: animal model, tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI), myocardial infarction model, nitroglycerin.
Language of Text: Chinese.

Xiao, L., D. Chartier, W. Han, Z. Wang, and S. Nattel (2003). **Gender-based transmural differences in canine cardiac repolarization.** *Journal of the American College of Cardiology* 41(6 Supplement A): 112A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, cardiac repolarization, gender based transmural differences.

Xing, D., A.L. Kjolbye, M.S. Nielsen, J.S. Petersen, K.W. Harlow, N.H. Holstein Rathlou, and J.B. Martins (2003). **Zp123 increases gap junctional conductance and prevents reentrant ventricular tachycardia during myocardial ischemia in open chest dogs.** *Journal of Cardiovascular Electrophysiology* 14(5): 510-520. ISSN: 1045-3873.

Abstract: ZP123 Prevents Ventricular Tachycardia. Introduction: The aim of this study was to determine if the stable antiarrhythmic peptide (AAP) analogue ZP123 increases gap junctional intercellular conductance and prevents reentrant ventricular tachycardia (VT) during coronary artery occlusion. Methods and Results: Voltage clamp experiments demonstrated that 10 nM ZP123 improved gap junctional intercellular conductance by 69% +- 20% in pairs of guinea pig ventricular myocytes. VT was induced by programmed stimulation in alpha-chloralose anaesthetized open chest dogs 1 to 4 hours after coronary artery occlusion. Three-dimensional activation mapping was done using six bipolar electrograms on each of 23 multipolar needles in the risk zone. When VT was reproducibly induced, dogs were randomly assigned to receive either saline or ZP123 cumulatively at three dose levels (intravenous bolus followed by 30-min infusion per dose). Attempts to induce VT were repeated in each infusion period. Mass spectrometry was used to measure ZP123 plasma concentrations. Twenty-six dogs with reentrant VT were included. ZP123 significantly prevented reentrant VT at all plasma concentrations vs saline: 1.0 +- 0.2 nM: 6/12 vs 0/12; 7.7 +- 0.6 nM: 7/13 vs 1/12; and 69.2 +- 5.4 nM: 9/13 vs 1/13. The preventive effect of ZP123 on reentrant VT was closely correlated to reversal of functional, unidirectional conduction block. ZP123 did not affect effective refractory period, surface ECG parameters, mean arterial pressure, or infarct size. Conclusion: The stable AAP analogue ZP123 increased gap junctional intercellular conductance and specifically prevented the induction of reentrant VT during ischemia in a broad dose range without proarrhythmic or hemodynamic side effects. ZP123 is a promising candidate for use in preventing ischemia-induced VT.

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, coronary artery occlusion, heart disease, vascular disease, prevention and control, myocardial ischemia, reentrant ventricular tachycardia, gap junctional conductance.

Xiong, W., F.G. Akar, A.A. Armoundas, I.A. Hobai, B. O'rourke, and G.F. Tomaselli (2004). **Na/ca exchange stoichiometry in control and failing canine ventricle.** *Biophysical Journal* 86(1): 551A. ISSN: 0006-3495.

NAL Call Number: 442.8 B5238

Abstract: Na/Ca exchange (NCX) is an essential modulator of Ca homeostasis and contractile function in the heart. The NCX stoichiometry is of considerable interest, but little is known about whether the stoichiometry is altered in heart failure. We investigated the NCX stoichiometry in myocytes isolated from the left ventricular mid-wall of pacing-tachycardia induced failing hearts and control hearts. NCX current was measured in patch-clamped myocytes perfused with solutions of varying extracellular Na or Ca concentrations over a range of holding potentials under conditions that blocked all other known transmembrane Na+ and Ca2+ flux. Analysis of the relationship between the reversal potential and extracellular (Na+) or (Ca2+) in normal cells yielded coupling ratios of 1.90+-0.02 Na+ per net charge (corresponding to 4.22 Na+: 1 Ca2+) and 0.52+-0.01 Ca2+ per net charge (3.92 Na+: 1 Ca2+), consistent with a stoichiometry of 4 Na+ to 1 Ca2+ per transport cycle. Neither a reduction

in intracellular (Na+) from 20 to 10 mM nor a change of the holding potential from 0 to -60 mV altered the stoichiometry of NCX. The coupling ratios were 1.87+-0.04 Na+ per net charge (4.29 Na+: 1 Ca2+) and 0.50+-0.03 Ca2+ per net charge (4.00 Na+: 1 Ca2+) in myocytes from failing ventricles. However, when intracellular (Na+) was reduced to 5 mM, the NCX stoichiometry changed to 3.06 Na+: 1 Ca2+ and 3.15 Na+: 1 Ca2+ in normal and failing cells, respectively. We conclude that the stoichiometry of NCX varies from 3:1 at lower intracellular (Na+) to 4:1 at higher intracellular (Na+). The stoichiometries do not differ in patch-clamped ventricular myocytes from control and failing hearts. Nevertheless, if there is an increase in intracellular (Na+) in heart failure, it is likely that the stoichiometry of NCX could be altered in failing myocytes.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, heart failure, heart disease, sodium, calcium exchange, stoichiometry.

Xu, H.B. and Z.Q. Huang (2007). **Vasorelaxant effects of icariin on isolated canine coronary artery.** *Journal of Cardiovascular Pharmacology* 49(4): 207-13. ISSN: 0160-2446.
Abstract: Owing to its cardiovascular therapeutical effects, icariin, a flavonoid isolated from Epimedii herba, is considered to be the major active constituent of Epimedii herba. The aim of this study is to investigate the effect of icariin on precontracted coronary artery isolated from canine. Coronary artery segments were isolated from normal anesthetized Beagle dogs and cut into 5-mm rings. The rings were mounted in an organ chamber and contracted by either 40 mM KCl or 10 microM PGF2alpha, and vasorelaxant tone to icariin was measured. Treatment of icariin could significantly produce a relaxation of precontracted coronary arterial rings with intact endothelium in a concentration-dependent manner. Comparatively, the vasorelaxation disappeared in denuded-endothelium rings. Furthermore, the vasorelaxant effect of icariin was blocked by Nomega-Nitro- L-arginine Methyl Ester (L-NAME), 1H-[1, 2, 4]-oxadiazolo [4, 3-a] quinoxalin-1-one (ODQ) but not by indomethacin and glibenclamide, respectively. Tetraethylammonium (TEA) could partly antagonize the vasorelaxant effect triggered by icariin. There was no significant gene expression difference of the endothelial nitric oxide synthase (eNOS) gene in coronary arterial rings among the different concentrations of icariin by RT-PCR, but the activity of eNOS was increased in a concentration-dependent manner after icariin exposure. These results suggest that icariin produces NO-dependent relaxation in the isolated canine coronary artery, and the possible mechanism is involved in the activation of eNOS protein and NO-cGMP pathway.
Descriptors: coronary vessels drug effects, drugs, chinese herbal pharmacology, flavonoids pharmacology, vasodilation drug effects, analysis of variance, anti arrhythmia agents pharmacology, coronary vessels enzymology, coronary vessels physiopathology, dinoprost pharmacology, dogs, dose response relationship, drug, endothelium, vascular drug effects, endothelium, vascular enzymology, endothelium, vascular physiopathology, enzyme inhibitors pharmacology, glyburide pharmacology, indomethacin pharmacology, models, animal, ng nitroarginine methyl ester pharmacology, nitric oxide synthase type iii drug effects, nitric oxide synthase type iii genetics, nitric oxide synthase type iii metabolism, oxadiazoles pharmacology, oxytocics pharmacology, potassium channel blockers pharmacology, quinoxalines pharmacology, rna, messenger drug effects, rna, messenger metabolism, reverse transcriptase polymerase chain reaction, tetraethylammonium pharmacology, vasodilation genetics.

Yada, T., H. Shimokawa, O. Hiramatsu, M. Goto, and F. Kajiya (2003). **Protective role of hydrogen peroxide, an endogenous edhf, in ischemia-reperfusion injury in canine coronary microcirculation in vivo.** *Circulation* 108 (17 Supplement): IV-226. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation.

Yada, T., H. Shimokawa, O. Hiramatsu, M. Goto, Y. Ogasawara, and F. Kajiya (2003). **Beneficial effects of hydroxyfasudil, a specific rho-kinase inhibitor, on ischemia-reperfusion injury in canine coronary microcirculation in vivo.** *Circulation* 108(17 Supplement): IV-226. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Descriptors: cardiovascular system, transport and circulation, pharmacology.

Yang Guirong , Zhang Wei , Wang Sujia , and Et Al (2003). **Echocardiographic monitering: a chronic canine atrial fibrillation model.** *Zhongguo Chaosheng Yixue Zazhi* 19(9): 641-643. ISSN: 1002-0101.
Abstract: Objective: To investigate the value of echocardiography in monitering a canine atrial fibrillation (AF) model with chronic rapid atrial pacing. Methods: Implantable pacemaker delivered 350apprx430 bpm stimuli to pace the right atrial appendage in 11 mongrel dogs for 8 weeks. Programmed electrical stimulation was performed before and after pacing. Changes of biatrial area and volume were assessed using echocardiography before rapid pacing and 1, 4, 8 weeks later. Results: The experiment was complete in 8 dogs. When pacemaker stopped, atrial fibrillation occurred spontaneously in 2 dogs. AF was induced by programmed stimulation in 4 dogs and by burst stimulation in 2 dogs. Biatrial area was significently enlarged after pacing 1 week while biatrial volume began to increase 4 weeks later. Mitral regurgitation and tricuspid regurgitation were noted in all dogs at the end of pacing. Conclusions: The canine model of chronic AF was established successfully. It is suggested that echocardiography be a valuable noninvasive monitoring method during the establishment.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, veterinary medicine, medical sciences, atrial fibrillation, heart disease, chronic rapid atrial pacing, heart disease, mitral regurgitation, tricuspid regurgitation, echocardiographic monitoring, clinical techniques, diagnostic techniques, implantable pacemaker, prosthetic, programmed electrical stimulation.
Language of Text: Chinese.

Yang, X.P. and S. Chiba (2003). **Interaction between neuropeptide y y1 receptors and alpha1b-adrenoceptors in the neurovascular junction of canine splenic arteries.** *European Journal of Pharmacology* 466(3): 311-315. ISSN: 0014-2999.
NAL Call Number: QP901.E8
Abstract: Previous study has demonstrated that periarterial electrical nerve stimulation (30-s trains of pulses at a frequency of 1 or 4 Hz) induces a double-peaked vasoconstriction consisting of an initial transient, predominantly P2X-receptor-mediated constriction followed by a prolonged, mainly alpha1-adrenoceptor-mediated response in the isolated canine splenic artery. Treatment with 8-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-8-azaspiro(4.5)

decane-7,9-dione (BMY 7378, 0.1 mumol/l), a selective alpha1D-adrenoceptor antagonist, produced a slight but significant inhibition of the second peaked responses. A marked inhibition of second peaked responses was obtained by exposure of the tissues to chloroethylclonidine (60 mumol/l), an alpha1B- and alpha1D-adrenoeptor antagonist. Neither BMY 7378 nor chloroethylclonidine affected the first peaked vasoconstrictor responses. (Leu31,Pro34)Neuropeptide Y (10-30 nmol/l), a selective neuropeptide Y Y1 receptor agonist, enhanced the second peaked responses in the presence of BMY 7378 but failed to enhance the responses in the presence of chloroethylclonidine. The results indicate that the postjunctional alpha1B-adrenoceptor subtype is likely coupled to neuropeptide Y Y1 receptors responsible for the cooperation of the sympathetic adrenergic and neuropeptide Yergic transmission in the canine splenic artery.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology.

Yao, G.H., F. Li, C. Zhang, P.F. Zhang, M. Zhang, Y.X. Zhao, X.N. Li, S.F. Ding, L. Zhong, and Y. Zhang (2007). **How many planes are required to get an accurate and timesaving measurement of left ventricular volume and function by real-time three-dimensional echocardiography in acute myocardial infarction?** *Ultrasound in Medicine and Biology* 33(10): 1572-8. ISSN: 0301-5629.
NAL Call Number: QC244.U4
Abstract: To derive the optimal cutting planes of real-time 3-D echocardiography (RT-3DE) for measuring left ventricular volume and ejection fraction (EF) in the presence of left ventricular regional wall motion abnormalities, 14 open-chest dogs were studied with RT-3DE full volume imaging and 2-D echocardiography (2DE) after left anterior descending coronary arteries were occluded for 90 min. Left ventricular end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) and EF were measured off-line with 2DE and RT-3DE (2-, 4- and 8-plane) methods. The autopsy EDV was estimated by the volume of saline solution injected into the excised heart and served as the reference volume (RefV) for comparison with EDV measured by 2DE and RT-3DE. Agreement analysis was performed according to the method of Bland and Altman. There were excellent correlations between 2DE, RT-3DE (2-plane) and RT-3DE (4-plane) methods on one hand, and RT-3DE (8-plane) method on the other in the measurements of EDV, ESV and SV ($r = 0.84$-0.99). However, 2DE and RT-3DE (2-plane) measurements significantly underestimated RT-3DE (8-plane) ($p < 0.01$), whereas no significant differences between RT-3DE (4-plane) and RT-3DE (8-plane) were found in terms of EDV, ESV and SV measurements. The values of EF determined by 2DE, RT-3DE (2-plane) and RT-3DE (4-plane) methods correlated highly with that by RT-3DE (8-plane) ($r = 0.82$-0.98) and there was no significant difference between the two measurements. EDV values determined by 2DE, RT-3DE (2-plane), RT-3DE (4-plane) and RT-3DE (8-plane) correlated highly with RefV ($r = 0.84$, $r = 0.92$, $r = 0.94$ and $r = 0.97$, respectively) and there was no significant difference between RefV and EDV by RT-3DE (4-plane) and RT-3DE (8-plane). In contrast, EDV measured by 2DE and RT-3DE (2-plane) methods underestimated RefV significantly ($p < 0.01$). In conclusion, RT-3DE allows reliable and reproducible measurement of left ventricular volume and EF, even in the presence of left ventricular regional wall motion abnormalities. RT-3DE (4-plane) is the method of choice for an accurate and timesaving quantification of left ventricular

volume and function.
Descriptors: echocardiography, three dimensional methods, myocardial infarction ultrasonography, ventricular dysfunction, left ultrasonography, dogs, echocardiography, heart ventricles ultrasonography, animal models.

Yeh, H.I., Y.J. Lai, Y.N. Lee, Y.J. Chen, Y.C. Chen, C.C. Chen, S.A. Chen, C.I. Lin, and C.H. Tsai (2003). **Differential expression of connexin43 gap junctions in cardiomyocytes isolated from canine thoracic veins.** *Journal of Histochemistry and Cytochemistry* 51(2): 259-266. ISSN: 0022-1554.
NAL Call Number: 381 J8222
Abstract: We investigated the phenotypic features of cardiomyocytes, including the gap junctions, in the myocardial sleeve of thoracic veins. Single cardiomyocytes, isolated from the canine pulmonary veins (PV) and superior vena cava (SVC) using digestive enzymes, were examined by immunoconfocal microscopy using antisera against connexin43 (Cx43), Cx40, and other cell markers. The results showed that isolated cardiomyocytes displayed rod shapes of various sizes, ranging from <50 mum to >200 mum in length, and all the cells expressed alpha-actinin and vinculin. Gap junctions made of various amounts of Cx43 and Cx40 were found at the cell borders. These two connexins were extensively co-localized. Comparison between the thoracic veins showed that cells of the SVC contained more Cx43 gap junctions (total Cx43 gap junctions area per cell surface area, 4.0+-0.2% vs 1.5+-0.2%; p<0.01). In addition, for single-nucleus cells, those from the PV were longer (103.7+-3.6 vs 85.0+-3.1 mum; p<0.01) but narrower (14.4+-0.5 vs 16.9mu0.9 mum; p<0.01). In conclusion, canine thoracic veins contain cardiomyocytes with differences in shape and gap junctions, suggesting that the electrical conduction properties may be different between the thoracic veins.
Descriptors: cardiovascular system, transport and circulation, cell biology, immunoconfocal microscopy, imaging and microscopy techniques, immunologic techniques, laboratory techniques.

Yelmen, N.K., G. Sahin, and T. Oruc (2004). **The effects of vagal stimulation on laryngeal vascular resistance and intraluminal pressure in the dog**. *Tohoku Journal of Experimental Medicine* 202(4): 283-294. ISSN: 0040-8727.
Abstract: In anaesthetized dogs (sodium pentobarbitone 30 mg/kg, i.v.) laryngeal vascular resistance was measured by unilateral perfusion at constant flow of the branch of the cranial superior thyroid artery that supplies the larynx. Arterial perfusion was at constant flow and inflow pressure was divided by flow to give laryngeal vascular resistance (RLV). Intraluminal laryngeal pressure (PL) and systemic arterial blood pressure (BP) were also measured. Stimulation (20 V, 20 Hz, 0.2 milliseconds) of the central end of cervical vagus caused an increase in RLV (+22.9+/-6.1%) and a decrease in PL (-12.1+/-4.4%). Stimulation (10 V, 10 Hz, 0.2 milliseconds) of the central end of the recurrent laryngeal nerve (RLN) reduced RLV (-3.4+/-0.8%) and PL (-7.5+/-4.1%). Stimulation of the peripheral end of the RLN decreased RLV (-7.1+/-1.9%) and increased PL (+21.6+/-7.7%). Stimulation of the central end of the superior laryngeal nerve (SLN) increased RLV (+17.9+/-3.2%) and PL (+59.8+/-2.7%), whereas stimulation of the peripheral end of the SLN decreased RLV (-4.8+/-1.6%) and PL (-4.1+/-2.4%). After treatment with alpha-adrenoreceptor antagonist phentolamine (0.5 mg/kg, Lv.), stimulation of the central end of cervical vagus nerve reduced RLV by 25% and decreased

BP. Phentolamine caused a decrease in BP and reduced the magnitude of increase in RLV in response to stimulation of central end of SLN. After atropine sulphate (0.5-2.0 mg/kg, i.v.), the stimulation of both central and peripheral ends of RLN reduced RLV. The decrease in RLV during stimulation of peripheral end of SLN was reduced by atropine. Thereafter, pancuronium bromide (0.06-0.1 mg/kg, i.v.) was given and dogs were artifically ventilated. After paralyzed, stimulation of the central end of the SLN decreased RLV (+26.0+/-4.5%) but produced no change in PL. It is concluded that parasympathetic motor fibers in the RLN and SLN are effective for the laryngeal vascularity and non-adrenergic system may be responsible for laryngeal vasoconstriction.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, vagal stimulation, clinical techniques, therapeutic and prophylactic techniques, intraluminal pressure, laryngeal vascular resistance, systemic arterial blood pressure.

Yelmen, N.K., G. Sahin, T. Oruc, and M. Hacibekiroglu (2003). **Hypoxic initiation of pulmonary hypertension is mediated by serotonin secretion from neuroepithelial bodies in chemodenervated dogs.** *Chinese Journal of Physiology* 46(1): 27-33. ISSN: 0304-4920.

Abstract: The purpose of this study was to investigate the stimulatory effect of hypoxia on the secretion of serotonin by neuroepithelial bodies (NEB) as well as to determine the relation between its level and changes in pulmonary arterial pressure (PAP) and also to determinate the effect of serotonin antagonists (pizotifen and methysergide) on the responses of pulmonary and systemic arterial pressures. The experiments were carried out in peripheral chemoreceptor-denervated dogs anesthetized with Na penthabarbital (30 mg/kg i.v.). On the breathing of normoxic and hypoxic (7% O2-93% N2) gas mixtures and on the injection of KCN (80 mug/kg i.v.), PAP, systemic arterial blood pressure (BP), tidal volume (VT), respiratory frequency (f/min), ventilation minute volume (VE) were determined. Also PAP and BP were recorded before and after the injection of pizotifen (0.5 mg/kg i.v.) and methysergide (1 mg/kg i.v.) during normoxic or hypoxic gas mixture breathing. At the end of each experimantal phase, serotonin level, PaO2, PaCO2 and pHa values in blood samples obtained from left ventricle and femoral artery were determined. On the breathing of the hypoxic gas mixture of the chemodenervated dogs, VT, VE and BP significantly decreased ($P<0.001$, $P<0.001$, $P<0.01$). The mean value of PAP and serotonin levels (ventricular and femoral) were found significantly increased when compared with the corresponding normoxic values ($P<0.001$, $P<0.05$). On the other hand, injection of KCN produced no significant changes in PAP, serotonin levels, BP and respiratory parameters. After the injection of pizotifen, PAP was significantly increased in hypoxia ($P<0.01$). After the injection of methysergide, the response of PAP was completely abolished during the breathing of hypoxic gas mixture. The finding of the abolition of response of PAP to hypoxia after the injection of methysergide indicates that serotonin release from NEB may be responsible for the elevation of PAP in hypoxic hypoxia.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, respiratory system, respiration, veterinary medicine, medical sciences, hypoxia, respiratory system disease, pulmonary hypertension, chemodenervation, experimental surgical techniques, laboratory techniques, pulmonary arterial pressure [pap].

Yu, S., Y. Ma, T. Xia, and S. Ma (1995). **Studies of action of rhodobrun roseum limpr on changes of red cell aggregation and yield-shear stress in dogs with acute experimental coronary occlusion**. *Zhongguo Zhongyao Zazhi* 20(7): 429-431, 449. ISSN: 1001-5302.
Abstract: Following acute occlusion of the left anterior descending coronary artery in dogs, significant increases were observed in the red cell aggregation index, yield-shear stress and red cell electrophoretic time in blood drained from ischemic area. When transfusion was performed with Rhodobrum roseum solution from the right femoral vein, significant rises of the above-said items were observed.
Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, cell biology, pharmacognosy, pharmacology, blood viscosity, myocardial ischemia.
Language of Text: Chinese.

Zhang, J., Z. Chen, F.R. Cobb, and J.S. Stamler (2004). **Role of mitochondrial aldehyde dehydrogenase in nitroglycerin-induced vasodilation of coronary and systemic vessels - an intact canine model**. *Circulation* 110(6): 750-755. ISSN: 0009-7322.
NAL Call Number: RC681.A1 C8
Abstract: Background-It has recently been shown that mitochondrial aldehyde dehydrogenase 2 (mtALDH) catalyzes the formation of 1,2-glyceryl dinitrate and nitrite from nitroglycerin (glyceryl trinitrate (GTN)) within mitochondria, leading to production of cGMP and vasorelaxation. However, whether this mechanism operates in the systemic and coronary beds that subserve the antianginal action of GTN is not known. In this study, we address this question in an intact canine model. Methods and Results-Fourteen healthy mongrel dogs (weight, 20 to 25 kg) were studied. Coronary blood flow and hemodynamics were continuously monitored by a pulse Doppler flow probe implanted around the left circumflex coronary artery and with catheters in left ventricle and aorta, respectively. Each dog was given a 1-mL bolus injection of GTN, sodium nitroprusside (SNP), or adenosine through a catheter in the left atrium before and 30 minutes after infusion of cyanamide (17 mg/kg), an inhibitor of mtALDH. Cyanamide significantly inhibited both the classic dehydrogenase and GTN reductase activities of mtALDH in situ and attenuated the coronary blood flow increase and declines in blood pressure and left ventricular end-diastolic pressure produced by GTN in vivo. In contrast, mtALDH inhibition had no effect on the coronary and systemic effects of SNP and adenosine. Conclusions-Our data suggest that mtALDH contributes to GTN biotransformation in vivo and thus at least partly underlies the antianginal mechanism of drug action. Our findings also highlight the differences in biometabolism of clinically relevant nitrosovasodilators.
Descriptors: cardiovascular system, transport and circulation, pharmacology.

Zhang Shunye , Sun Zongquan , Liu Lixin , and Hasichaonu (2003). **Carvedilol attenuates cpb-induced apoptosis in dog heart: regulation of fas/fasl and caspase-3 pathway.** *Chinese Medical Journal (English Edition)* 116(5): 761-766. ISSN: 0366-6999.
Abstract: Objective: To evaluate the effects of Carvedilol on cardiopulmonary bypass (CPB)-induced myocardiocyte apoptosis and its effects on regulation of Fas, FasL expression, caspase-3 activity and oxidative stress in the left ventricle (LV) in this setting. Methods: Ten adult dogs undergoing conventional hypothermic CPB were randomly divided into

control and Carvedilol treated groups (n=5, respectively). Dogs in Carvedilol treated group received a bolus of Carvedilol (1 mg/kg) intravenously and a maintenance dosage of Carvedilol (3 mugcntdotmin-1cntdotkg-1) for 3 hours after the reperfusion of the heart. Dogs in control group received no Carvediolol. LV samples were obtained before, during and 3 hours after CPB. In situ nick end-labeling (TUNEL) technique was used to detect the apoptotic cells. The expressions of Fas and FasL were detected immunohistochemically and quantified by fluorescence activated cell sorting (FACS). The activity of caspase-3 enzyme and malondialdehyde (MDA) level were measured by cleavage of Z-DEVD-AMC substrate and thiobarbituric acid reactive substance (TBARS) method, respectively. Results: Before and during CPB, all the parameters were not significantly different intra- or between groups (P>0.05). After CPB, these parameters in both groups were significantly elevated compared with those of before and during CPB (P<0.028, respectively). However, the number of apoptotic cells in Carvedilol treated group was significantly decreased compared with that of the control group (P<0.021). The expressions of Fas and FasL were significantly downregulated by Carvedilol (P<0.001 and 0.003, respectively). The caspase-3 activity and the content of MDA in the Carvedilol treated group was also significantly reduced (P<0.026 and 0.005, respectively). Conclusions: Carvedilol significantly reduces CPB-induced cardiomyocyte apoptosis in dog hearts and the reduction of cardiomyocyte apoptosis is associated with downregulation of Fas and FasL expression, inhibition of caspase-3 activity and oxidative stress in LV.

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, surgery, medical sciences, tunel, genetic techniques, laboratory techniques, cardiopulmonary bypass, clinical techniques, therapeutic and prophylactic techniques, apoptosis, oxidative stress.

Zhang, X., S. Kinugawa, and T. Hintze (2004). **Impaired endothelial nitric oxide production from coronary microvessels induced by camp signal transduction in diabetic dog heart**. *FASEB Journal* 18(4-5): Abst. 201.6. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, diabetes, endocrine disease, pancreas, metabolic disease, cyclic amp signal transduction, posttranslational problem.

Zhou, S., B.C. Jung, A.Y. Tan, V.Q. Trang, G. Gholmieh, S.W. Han, S.F. Lin, M.C. Fishbein, P.S. Chen, and L.S. Chen (2008). **Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death.** *Heart Rhythm the Official Journal of the Heart Rhythm Society* 5(1): 131-9. ISSN: 1547-5271.

Abstract: BACKGROUND: Little information is available on the temporal relationship between instantaneous sympathetic nerve activity and ventricular arrhythmia in ambulatory animals. OBJECTIVE: The purpose of this study was to determine if increased sympathetic nerve activity precedes the onset of ventricular arrhythmia. METHODS: Simultaneous continuous long-term recording of left stellate ganglion (LSG) nerve activity and electrocardiography was performed in eight dogs with nerve growth factor infusion to the LSG, atrioventricular block, and myocardial infarction (experimental group) and in six normal

dogs (control group). RESULTS: LSG nerve activity included low-amplitude burst discharge activity (LABDA) and high-amplitude spike discharge activity (HASDA). Both LABDA and HASDA accelerated heart rate. In the experimental group, most ventricular tachycardia (86.3%) and sudden cardiac death were preceded within 15 seconds by either LABDA or HASDA. The closer to onset of ventricular tachycardia, the higher the nerve activity. The majority of HASDA was followed immediately by either ventricular arrhythmia (21%) or QRS morphology changes (65%). HASDA occurred in a circadian pattern. HASDA occurred twice as often in the experimental group than in the control group. Electrical stimulation of LSG increased transmural heterogeneity of repolarization (Tpeak-end intervals) and induced either ventricular tachycardia or fibrillation in the experimental group but not in the control group. Immunohistochemical studies revealed increased synaptogenesis and nerve sprouting in the LSG in the experimental group. CONCLUSION: Two distinct types of LSG nerve activity (HASDA and LABDA) are present in the LSG of ambulatory dogs. The majority of malignant ventricular arrhythmias are preceded by either HASDA or LABDA, with HASDA particularly arrhythmogenic.
Descriptors: death, sudden, cardiac prevention and control, stellate ganglion physiology, sympathetic nervous system physiopathology, tachycardia, ventricular physiopathology, ventricular fibrillation physiopathology, dogs, electric stimulation, electrocardiography, electrophysiology, heart rate, models, animal, tachycardia, ventricular etiology, time factors, ventricular fibrillation etiology.
Notes: Comment In: Heart Rhythm. 2008 Jan;5(1):140-1.

Zhu, B.M., S. Miyamoto, Y. Nagasawa, T. Wajima, and K. Hashimoto (2003). **Effect of the sarcolemmal katp channel blocker hmr1098 on arrhythmias induced by programmed electrical stimulation in canine old myocardial infarction model: comparison with glibenclamide.** *Journal of Pharmacological Sciences* 93(1): 106-113. ISSN: 1347-8613.
Abstract: The blockade of myocardial KATP channels may be antiarrhythmic for ischemic arrhythmias. A new sulfonylthiourea, HMR1098 (1-(15-(2-(5-chloro-o-anisamido) ethyl)-2-methoxyphenylsulfonyl)-3-methylthiourea, sodium salt), was demonstrated to be a cardioselective KATP-channel antagonist and to suppress arrhythmias during acute ischemia. We investigated effects of HMR1098 on the arrhythmias induced by programmed electrical stimulation (PES) in a canine old myocardial infarction model. HMR1098 (3 mg/kg, i.v.) significantly improved the scores of PES-induced ventricular arrhythmias, without changing the blood glucose concentrations. A classical sulfonylurea, glibenclamide (1 mg/kg, i.v.), had no significant effects on these arrhythmias, but reduced the blood glucose and increased the plasma insulin concentrations.
Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemic arrhythmia, heart disease, vascular disease, old myocardial infarction, heart disease, programmed electrical stimulation induced ventricular arrhythmia, heart disease.

Ziba, T., C.W. Smith, and C.A. Rivera (2004). **Detection of extra-nuclear high mobility group box-1 protein in a canine model of myocardial infarction**. *FASEB Journal* 18(4-5): Abst. 670.16. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: box-1 protein (HMGB-1), nuclear protein , biochemistry and molecular bio-

physics, cardiovascular system, transport and circulation, myocardial infarction, heart disease, vascular disease

Zong, P., S. Setty, W. Sun, J.D. Tune, and H.F. Downey (2004). **Alpha -adrenergic right coronary vasoconstriction forces mobilization of right ventricular oxygen extraction reserve in exercising dogs**. *FASEB Journal* 18(4-5): Abst. 200.1. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation.

Dental and Oral

Al Nawas, B., K.A. Groetz, H. Goetz, H. Duschner, and W. Wagner (2008). **Comparative histomorphometry and resonance frequency analysis of implants with moderately rough surfaces in a loaded animal model.** *Clinical Oral Implants Research* 19(1): 1-8. ISSN: 0905-7161.

Abstract: OBJECTIVES: Test of favourable conditions for osseointegration with respect to optimum bone-implant contact (BIC) in a loaded animal model. The varied parameters were surface roughness and surface topography of commercially available dental implants. METHOD: Thirty-two implants of six types of macro and microstructure were included in the study (total 196). The different types were: minimally rough control: Branemark machined Mk III; oxidized surface: TiUnite MkIII and MkIV; ZL Ticer; blasted and etched surface: Straumann SLA; rough control: titanium plasma sprayed (TPS). Sixteen beagle dogs were implanted with the whole set of the above implants. After a healing period of 8 weeks, implants were loaded for 3 months. For the evaluation of the BIC areas, adequately sectioned biopsies were visualized by subsurface scans with confocal laser scanning microscopy (CLSM). RESULTS: The primary statistical analysis testing BIC of the moderately rough implants (mean 56.1+/-13.0%) vs. the minimally rough and the rough controls (mean 53.9+/-11.2%) does not reveal a significant difference (P=0.57). Mean values of 50-70% BIC were found for all implant types. Moderately rough oxidized implants show a median BIC, which is 8% higher than their minimally rough turned counterpart. The intraindividual difference between the TPS and the blasted and etched counterparts revealed no significant difference. The turned and the oxidized implants show median values of the resonance frequency [implant stability quotients (ISQ)] over 60; the nonself-tapping blasted and etched and TPS implants show median values below 60. DISCUSSION: In conclusion, the benefit of rough surfaces relative to minimally rough ones in this loaded animal model was confirmed histologically. The comparison of different surface treatment modalities revealed no significant differences between the modern moderately rough surfaces. Resonance frequency analysis seems to be influenced in a major part by the transducer used, thus prohibiting the comparison of different implant systems.

Descriptors: dental implants, dental prosthesis design, osseointegration, endosseous, dental restoration failure, dogs, experimental, microscopy, confocal, models, animal, statistics, nonparametric, surface properties, vibration.

Alexander, H., J.L. Ricci, and G.J. Hrico (2009). **Mechanical basis for bone retention around dental implants.** *Journal of Biomedical Materials Research. Part B, Applied Biomaterials* 88(2): 306-11.

Abstract: This study, analytically, through finite element analysis, predicts the minimization of crestal bone stress resulting from implant collar surface treatment. A tapered dental implant design with (LL) and without (control, C) laser microgrooving surface treatment are evaluated. The LL implant has the same tapered body design and thread surface treatment as the C implant, but has a 2-mm wide collar that has been laser micromachined with 8 and 12 microm grooves in the lower 1.5 mm to enhance tissue attachment. In vivo animal and

human studies previously demonstrated decreased crestal bone loss with the LL implant. Axial and side loading with two different collar/bone interfaces (nonbonded and bonded, to simulate the C and LL surfaces, respectively) are considered. For 80 N side load, the maximum crestal bone distortional stress around C is 91.9 MPa, while the maximum crestal bone stress around LL, 22.6 MPa, is significantly lower. Finite element analysis suggests that stress overload may be responsible for the loss of crestal bone. Attaching bone to the collar with LL is predicted to diminish this effect, benefiting crestal bone retention. Copyright 2007 Wiley Periodicals, Inc.
Descriptors: bone and bones cytology, dental implants, biomechanics, dogs, imaging, three dimensional, models, animal, wound healing.

Araujo, M., E. Linder, J. Wennstrom, and J. Lindhe (2008). **The influence of Bio-Oss Collagen on healing of an extraction socket: an experimental study in the dog.** *International Journal of Periodontics and Restorative Dentistry* 28(2): 123-35. ISSN: 0198-7569.
Abstract: The objective of the present experiment was to evaluate the effect on hard tissue modeling and remodeling of the placement of a xenograft in fresh extraction sockets in dogs. Five mongrel dogs were used. Two mandibular premolars (4P4) were hemisected in each dog, and the distal roots were carefully removed. In one socket, a graft consisting of Bio-Oss Collagen (Geistlich) was placed, whereas the contralateral site was left without grafting. After 3 months of healing, the dogs were euthanized and biopsies sampled. From each experimental site, four ground sections (two from the mesial root and two from the healed socket) were prepared, stained, and examined under the microscope. The presence of Bio-Oss Collagen failed to inhibit the processes of modeling and remodeling that took place in the socket walls following tooth extraction. However, it apparently promoted de novo hard tissue formation, particularly in the cortical region of the extraction site. Thus, the dimension of the hard tissue was maintained and the profile of the ridge was better preserved. The placement of a biomaterial in an extraction socket may promote bone modeling and compensate, at least temporarily, for marginal ridge contraction.
Descriptors: bone substitutes therapeutic use, collagen therapeutic use, minerals therapeutic use, tooth socket surgery, alveolar process pathology, alveolar process surgery, bicuspid surgery, biopsy, bone remodeling drug effects, connective tissue pathology, dogs, epithelial attachment pathology, mandible pathology, mandible surgery, models, animal, osteogenesis drug effects, periodontium pathology, surgical flaps, time factors, tooth extraction, tooth socket pathology, transplantation, heterologous, wound healing drug effects.

Artzi, Z., N. Givol, M.D. Rohrer, C.E. Nemcovsky, H.S. Prasad, and H. Tal (2003). **Qualitative and quantitative expression of bovine bone mineral in experimental bone defects. Part 1: description of a dog model and histological observations.** *Journal of Periodontology* 74(8): 1143-1152. ISSN: 0022-3492.
Abstract: Background: The purpose of this study was to evaluate histologically the contribution of inorganic bovine bone biomaterial in a new experimental bone defect in dogs at different healing periods and to examine newly formed bone around the grafted mineral particles and their relationship in membrane-protected (test) and non-protected intrabony (control) defects. Methods: Four round intrabony defects, 5X4 mm were made bilaterally (at

different times) on the lateral bony mandibular angle in eight dogs. Two defects were filled with bovine bone mineral (BBM) particles and two remained non-grafted but were blood clotted. A collagen membrane covered each defect type (n=4). This procedure was repeated on the contralateral side at a different given time to obtain two different healing periods in each dog. Thus, four specimens were obtained at 3, 6, 12, and 24 months postoperatively for each healing period. The non-decalcification method (Donath technique) with Stevenel's blue and van Gieson's picro fuchsin staining was used for histological examination. Results: Newly formed bone was observed at all examined defect types. The BBM particles were clearly evident regardless of the healing period. At 3 and 6 months, newly formed bone, woven in nature, was incorporated with the grafted particles. High cellular bone with occasional osteoclasts was noted towards the surface of the mineral particles. No substantial difference was observed between the protected and the non-protected defects except for higher ossified centers around the membrane-protected defects. At the non-grafted sites, the membrane-protected defect showed newly formed bone near the bony walls, and particularly under the membrane, establishing a bony bridge over the defect at the healing periods. The non-grafted unprotected defect (control) showed bone formation only at the base and close to the bony walls leaving a healed concave configuration. At 1 and 2 years, the grafted sites showed full bone healing configuration. However, the grafted particles still dominated the previous defect area and were completely surrounded by the newly formed bone. Osteons and lamellar bone arrangement were established but the bone was still highly cellular and osteoclasts could still be identified. The non-grafted membrane-protected sites showed excellent bone healing although areas of non-mineralized soft tissue were often seen. The control sites healed but still presented with a concave surface configuration. Conclusions: BBM biomaterial is a highly osteoconductive material. In a 4-wall bony defect, newly formed bone was well evident in establishing excellent bone healing configuration with or without a regenerative biological barrier. The grafted material dominated the experimental sites with no substantial resorption at any healing period up to 2 years observation.

Descriptors: biomaterials, dental and oral system, ingestion and assimilation, skeletal system, movement and support, donath non decalcification method, laboratory techniques, stevenel's blue staining, histology and cytology techniques, collagen membrane, laboratory equipment, histology, histology and cytology techniques, inorganic bovine bone biomaterial, medical equipment, van gieson's picro fuchsin staining, bone formation, bony walls, concave surface configuration, grafted mineral particles, healing configuration, healing period, intrabony defect, membrane protected, non protected, ossified centers, osteoconduction.

Berglundh, T., I. Abrahamsson, M. Welander, N.P. Lang, and J. Lindhe (2007). **Morphogenesis of the peri-implant mucosa: an experimental study in dogs.** *Clinical Oral Implants Research* 18(1): 1-8. ISSN: 0905-7161.

Abstract: PURPOSE: The objective of the present experiment was to study the morphogenesis of the mucosal attachment to implants made of c.p. titanium. MATERIAL AND METHODS: All mandibular premolars were extracted in 20 Labrador dogs. After a healing period of 3 months, four implants (ITI Dental Implant System) were placed in the right and left sides of the mandible. A non-submerged implant installation technique was used and the mucosal tissues were secured to the conical marginal portion of the implants with interrupted

sutures. The sutures were removed after 2 weeks and a plaque control program including daily cleaning of the remaining teeth and the implants was initiated. The animals were sacrificed and biopsies were obtained at various intervals to provide healing periods extending from Day 0 (2 h) to 12 weeks. The mandibles were removed and placed in the fixative. The implant sites were dissected using a diamond saw and processed for histological analysis. RESULTS: Large numbers of neutrophils infiltrated and degraded the coagulum that occupied the compartment between the mucosa and the implant during the initial phase of healing. At 2 weeks after surgery, fibroblasts were the dominating cell population in the connective tissue interface but at 4 weeks the density of fibroblasts had decreased. Furthermore, the first signs of epithelial proliferation were observed in specimens representing 1-2 weeks of healing and a mature barrier epithelium occurred after 6-8 weeks of healing. The collagen fibers of the mucosa were organized after 4-6 weeks of healing. CONCLUSION: It is suggested that the soft-tissue attachment to implants placed using a non-submerged installation procedure is properly established after several weeks following surgery.
Descriptors: dental implants, morphogenesis physiology, periodontium growth and development, blood coagulation physiology, collagen, connective tissue growth and development, connective tissue pathology, dental materials, dogs, epithelial attachment growth and development, epithelial attachment pathology, epithelium growth and development, epithelium pathology, fibroblasts pathology, fibroblasts physiology, mandible surgery, models, animal, neutrophils pathology, neutrophils physiology, periodontium pathology, titanium, wound healing physiology.

Bernard, J.P., S. Szmukler Moncler, S. Pessotto, L. Vazquez, and U.C. Belser (2003). **The anchorage of Branemark and ITI implants of different lengths. I. An experimental study in the canine mandible.** *Clinical Oral Implants Research.* 14(5): 593-600. ISSN: 0905-7161.
Abstract: The anchorage of machined Branemark and ITI TPS-coated implants of various lengths was investigated in an animal model. Branemark fixtures 7 and 10 mm long and ITI implants 6 and 10 mm long were inserted in the mandible of dogs and were reverse-torqued after 3 months of healing. The failing mode was different for the two implant systems. For the ITI implants, loosening coincided with the peak reverse-torque values. For the Branemark fixtures, two reverse-torque values were identified and recorded, a 'start to rotate' and a peak value. The 'start to rotate' values for the 7 and 10 mm Branemark fixtures were 36.67 and 38.57 Ncm, respectively, the peak values were 61.88 and 69.13 Ncm. The increase in implant length from 7 to 10 mm did not significantly improve the anchorage. The mean reverse-torque values for the 6- and 10-mm ITI implants were 104.66 and 192.25 Ncm, respectively; the difference was statistically significant. The mean removal torque of the 6-mm ITI implant was higher than the 7- and 10-mm Branemark implants. It is suggested that the distinct anchorage magnitude and the distinct loosening patterns registered for both implant systems might be related to the various surface states. The latter might account for the different failure tendencies mentioned in the literature for short Branemark and ITI implants.
Descriptors: animal model, testing, oral implants, torque, failure tendencies, Branemark and ITI implants.

Brink, J., S.J. Meraw, and D.P. Sarment (2007). **Influence of implant diameter on surrounding bone.** *Clinical Oral Implants Research* 18(5): 563-8. ISSN: 0905-7161.

Abstract: OBJECTIVES: Implant osseointegration is dependent upon various factors, such as bone quality and type of implant surface. It is also subject to adaptation in response to changes in bone metabolism or transmission of masticatory forces. Understanding of long-term physiologic adjustment is critical to prevention of potential loss of osseointegration, especially because excessive occlusal forces lead to failure. To address this issue, wide-diameter implants were introduced in part with the hope that greater total implant surface would offer mechanical resistance. Yet, there is little evidence that variation in diameter translates into a different bone response in the implant vicinity. Therefore, this study aimed at comparing the impact of implant diameter on surrounding bone. MATERIAL AND METHODS: Twenty standard (3.75 mm) and 20 wide (5 mm) implants were placed using an animal model. Histomorphometry was performed to establish initial bone density (IBD), bone to implant contact (BIC) and adjacent bone density (ABD). RESULTS: BIC was 71% and 73%, whereas ABD was 65% and 52%, for standard and wide implants, respectively. These differences were not statistically different (P>0.05). Correlation with IBD was then investigated. BIC was not correlated with IBD. ABD was not correlated to IBD for standard implants (r2=0.126), but it was correlated with wide implants (r2=0.82). In addition, a 1 : 1 ratio between IBD and ABD was found for wide implants. It can be concluded, within the limits of this study, that ABD may be influenced by implant diameter, perhaps due to differences in force dissipation.

Descriptors: dental implants, dental prosthesis design, mandible physiology, maxilla physiology, osseointegration physiology, biomechanics, bone density physiology, dogs, mandible anatomy and histology, maxilla anatomy and histology, models, animal, prospective studies, random allocation, stress, mechanical, surface properties.

Byun, J.H., B.W. Park, J.R. Kim, and J.H. Lee (2007). **Expression of vascular endothelial growth factor and its receptors after mandibular distraction osteogenesis.** *International Journal of Oral and Maxillofacial Surgery* 36(4): 338-44. ISSN: 0901-5027.

Abstract: During distraction osteogenesis, angiogenic activity is essential for new bone formation. This study examined the expression of vascular endothelial growth factor (VEGF) and two of its receptors, Flt-1 (VEGFR-1) and Flk-1 (VEGFR-2), in cellular components after mandibular distraction osteogenesis. Unilateral mandibular distraction (0.5 mm twice per day for 10 days) was performed in six mongrel dogs. Two animals each were killed on days 7, 14 and 28 after completion of distraction. The distracted mandibular segments and contralateral undistracted control segments were harvested and processed for immunohistochemical examination. Seven days after distraction, there was a significant increase in the expression levels of VEGF and its receptors in the osteoblasts, osteocytes and immature fibroblast-like cells compared to control specimens. These levels were maintained for 14 days after distraction in the osteoblasts and fibroblast-like cells. Twenty-eight days after distraction, VEGF and VEGFR-1 were expressed only moderately/weakly in the osteoblasts, and no VEGFR-2 expression was detected in the cellular component of the distracted bone. Throughout the observation period, VEGFR-1 expression was stronger than that of VEGFR-2. The expression patterns of VEGF and its receptors suggest that it plays an important role

in osteogenesis, and that osteoblasts and immature fibroblast-like cells of the distracted bone may have an autocrine growth effect during distraction osteogenesis.
Descriptors: mandible surgery, osteogenesis, distraction, vascular endothelial growth factor a analysis, vascular endothelial growth factor receptor 1 analysis, vascular endothelial growth factor receptor 2 analysis, autocrine communication physiology, coloring agents diagnostic use, dogs, fibroblasts metabolism, immunohistochemistry, mandible cytology, mandible metabolism, models, animal, neovascularization, physiologic physiology, osteoblasts metabolism, osteocytes metabolism, osteogenesis physiology, time factors.

Choi, B.H., J. Li, H.S. Kim, C.Y. Ko, S.M. Jeong, and F. Xuan (2008). **Comparison of submerged and nonsubmerged implants placed without flap reflection in the canine mandible.** *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 105(5): 561-5.
Abstract: OBJECTIVE: The purpose of this study was to compare the bone healing around submerged and nonsubmerged implants installed in a canine mandible model using a flapless technique. STUDY DESIGN: Bilateral, edentulated, flat alveolar ridges were created in the mandibles of 6 mongrel dogs. After 3 months of healing, 2 implants were placed in 1 side by either miniflap submerged or flapless nonsubmerged procedures. After healing for an additional 8 weeks, microcomputerized tomography at the implantation site was performed. Osseointegration was calculated as the percent of the implant surface in contact with bone. Bone height was measured in the peri-implant bone. RESULTS: The mean osseointegration was greater (64.7%) in miniflap submerged sites than in the flapless nonsubmerged sites (56.8%; $P < .05$). The mean peri-implant bone height was greater (11.0 mm) in the miniflap submerged sites than in the flapless nonsubmerged sites (10.1 mm; $P < .05$). CONCLUSION: This study demonstrated that the submerged procedure was more effective than the nonsubmerged procedure in improving implant anchorage in the early phase after implant placement.
Descriptors: dental implantation, endosseous methods, dental implants, osseointegration, dental abutments, dental stress analysis, dogs, implants, experimental, mandible surgery, models, animal, random allocation, surgical flaps, tomography, x ray computed, wound healing.

Chung, S.H., S.J. Heo, J.Y. Koak, S.K. Kim, J.B. Lee, J.S. Han, C.H. Han, I.C. Rhyu, and S.J. Lee (2008). **Effects of implant geometry and surface treatment on osseointegration after functional loading: a dog study.** *Journal of Oral Rehabilitation* 35(3): 229-36.
Abstract: The purpose of this study was to evaluate the geometry and surface characteristics of osseointegration after functional loading by radiographic, periodontal and histomorphometric analyses. We analysed three groups of implants with different geometry and surface characteristics using experimental dogs. The control group received Branemark implants (group 1). Group 2 and group 3 implants each had a 0.5-mm pitch height but differed in surface characteristics. Group 2 implants were machine surfaced and group 3 implants were thermally oxidized at 800 degrees C for 2 h in a pure oxygen atmosphere. For these experiments, which used a total of four healthy beagle dogs, the implants were randomly installed into the extracted first, second and third premolar positions. The animals received radiographic and clinical periodontal examinations at 6 and 12 months post-loading, and were then killed for histomorphometric analysis. The radiographic analysis showed that mean

crestal bone resorption in the control group was greater than that observed in the experimental groups (P < 0.05). The percentage of bone-to-implant contact for group 3 (83.7%) was significantly higher than in groups 1 (74.4%) and 2 (75.0%) (P < 0.05). Overall, implant geometry and surface treatment affected the rate of crestal bone resorption and bone healing surrounding the dental implants.
Descriptors: dental implantation, endosseous, dental implants, dental prosthesis design, osseointegration, bone remodeling, dental plaque index, dental stress analysis, dogs, models, animal, periodontal index, titanium, tooth socket pathology, treatment outcome.

Coelho, P.G., G. Cardaropoli, M. Suzuki, and J.E. Lemons (2009). **Early healing of nanothickness bioceramic coatings on dental implants. An experimental study in dogs.** *Journal of Biomedical Materials Research. Part B, Applied Biomaterials* 88(2): 387-93.
Abstract: Thick bioceramic coatings like plasma sprayed hydroxyapatite have been shown to increase the overall tissue response and biomechanical fixation of dental implants. However, the presence and potential fracture of a bone-coating-metallic substrate interface at long times after implantation led these implants to fall from favor in clinical practice. The purpose of this study was to evaluate the biomechanical fixation and biological response of Ca- and P-based, 20-50 nm thickness bioceramic deposition on a previously alumina-blasted/acid-etched Ti-6Al-4V implant surface in a dog model. Cylindrical alumina-blasted/acid-etched (AB/AE) (Control, n = 16), and Nanothickness bioceramic coated AB/AE(Nano, n = 16) implant surfaces were surgically placed in dogs proximal tibia and remained for 2 and 4 weeks in vivo. Following euthanization, the implants-in-bone were mounted in epoxy and pullout at a 0.5 mm/min rate. Following mechanical testing, the specimens were decalcified and processed (Hematoxylin and Eosin) for standard transmitted light microscopy evaluation. Percent bone-to-implant contact (BIC) to the pulled out implant surface was determined through computer software. Statistical analyses were performed by one-way ANOVA at 95% level of significance and Tukey's post-hoc multiple comparisons. No significant differences in pullout force were observed (p > 0.88): 2W Control (212.08 +/- 42.96 N), 2W Nano (224.35 +/- 42.97 N), 4W Control (207.07 +/- 42.97 N), and 4W Nano (190.15 +/- 45.94 N). No significant differences in %BIC were observed (p > 0.94): 2W Control (72.66 +/- 8.51), 2W Nano (69.44 +/- 8.51), 4W Control (70.44 +/- 8.51), and 4W Nano (69.11 +/- 9.09). It is shown that 20-50 nm thickness bioceramic depositions onto previously alumina-blasted/acid-etched substrates did not improve the biomechanical fixation and the BIC at early implantation times, and studies concerning shorter and longer implantation times are recommended for confirmation or before a conclusion can be made. Copyright 2008 Wiley Periodicals, Inc.
Descriptors: dental implants, dental porcelain chemistry, dental porcelain metabolism, nanostructures chemistry, wound healing, bone and bones metabolism, dogs, microscopy, electron, scanning, models, animal, nanostructures ultrastructure, stress, mechanical, time factors.

Conner, K.A., R. Sabatini, B.L. Mealey, V.J. Takacs, M.P. Mills, and D.L. Cochran (2003). **Guided bone regeneration around titanium plasma-sprayed, acid-etched, and hydroxyapatite-coated implants in the canine model.** *Journal of Periodontology* 74(5): 658-668. ISSN: 0022-3492.

Abstract: Background: Endosseous dental implants with rough surfaces have been designed to improve early healing, especially in areas of poor bone or insufficient bone quantity. The aim of this study was to histomorphometrically assess the bone-to-implant contact on 3 different rough-surfaced implants following guided bone regeneration. Methods: Mandibular premolars and first molars were extracted in 12 dogs, and healing was allowed for 6 months. Six implant osteotomy sites were prepared, 3 per side, followed by the creation of 7.3 mm wide by 5 mm deep surgical defects in the coronal section of the osteotomy sites. Ten-mm long titanium screw-type implants with titanium plasma-sprayed (TPS), hydroxyapatite-coated (HA), or acid-etched (AE) surfaces were placed; the surrounding defects were filled with canine demineralized freeze-dried bone allograft; implants/grafts were covered with expanded polytetrafluoroethylene membranes; and the tissue was closed. Following a healing period of 4 months, the animals were sacrificed and mandibular blocks were harvested for histomorphometric analysis. Results: The mean percentage of bone-to-implant contact in the defect and non-defect areas for the different implant surfaces was: AE 16.24% defect, and 28.78% non-defect; TPS 25.08% defect, and 16.96% non-defect; and HA 48.25% defect and 26.60% non-defect. Within the defect, the mean difference in the bone-to-implant contact was significant for HA compared to TPS ($P<0.0001$) and HA versus AE ($P<0.0001$); TPS versus AE was not significant ($P=0.063$). In the non-defect areas, the mean difference in the bone-to-implant contact was significant for AE versus TPS ($P=0.010$); all other comparisons were not significant. There were 18 membrane exposures in the 72 implant sites. Data were analyzed again to assess the impact of membrane complications. Using a 1-way analysis of variance, the bone-to-implant contact was compared between the sites with and without membrane complications. No significant differences were seen in the defect areas or in the non-defect areas between the sites with and without membrane complications. Conclusion: In this study, the bone-to-implant contact in regenerated bone was greatest when an HA-coated implant was used.
Descriptors: biomaterials, dental and oral system, ingestion and assimilation, methods and techniques, skeletal system, movement and support, dental implants, prosthetic, guided bone regeneration, clinical techniques, therapeutic and prophylactic techniques, histomorphometric analysis, histology and cytology techniques, laboratory techniques, one way analysis of variance, mathematical and computer techniques, polytetrafluoroethylene membranes, prosthetic, titanium plasma sprayed acid etched hydroxyapatite coated implants, prosthetic, bone to implant contact, follow up studies, membrane complications.

Cutando, A., G. Gomez Moreno, C. Arana, G. Escames, and D. Acuna Castroviejo (2007). **Melatonin reduces oxidative stress because of tooth removal.** *Journal of Pineal Research* 42(4): 419-20. ISSN: 0742-3098.
Descriptors: melatonin therapeutic use, oxidative stress drug effects, tooth extraction adverse effects, dogs, gingiva drug effects, gingiva metabolism, glutathione metabolism, lipid peroxidation drug effects, melatonin administration and dosage, models, animal, reactive nitrogen species metabolism.

Dogan, A., A. Ozdemir, A. Kubar, and T. Oygur (2003). **Healing of artificial fenestration defects by seeding of fibroblast-like cells derived from regenerated periodontal ligament in a dog: a preliminary study.** *Tissue Engineering* 9(6): 1189-1196. ISSN: 1076-3279.

Abstract: The purpose of this study was to assess the seeding of fibroblast-like cells to promote periodontal healing in artificial fenestration defects in a dog. Fibroblast-like cells were cultured by incubating regenerated periodontal ligament tissue, that had been surgically taken, underneath a Teflon membrane. Fenestration defects were surgically induced on the maxillary canine and first molar teeth at a spacing of 5 to 5 mm. Passage 4 cells (2X105 cells) in autologous blood coagulum were placed on root surfaces in two defects; the remaining two defects were used as controls. Healing was evaluated histomorphometrically on postoperative day 42. The main periodontal healing pattern consisted of connective tissue adaptation in three of the four specimens including one control, with cementum formation at 9-12%; one control specimen that exhibited 100% cementum formation. New bone formation was greater in the cell-seeding group (84%) compared with control (39%). In the cell-seeding group, one specimen exhibited total regeneration of bone (100%); however, the connective tissue located between newly formed bone and the root surface was observed to adapt to the dentin surface, with limited cementum formation. Seeding of cells from periodontal ligament may be promising to promote periodontal regeneration, but needs to be investigated in further studies.
Descriptors: dental and oral system, ingestion and assimilation, skeletal system, movement and support, artificial fenestration defects, healing, preliminary study.

Ebadian, B., M. Razavi, S. Soleimanpour, and R. Mosharraf (2008). **Evaluation of tissue reaction to some denture-base materials: an animal study.** *Journal of Contemporary Dental Practice* 9(4): 67-74.

Abstract: AIM: Controversy continues regarding the biocompatibility of denture base materials. One method to evaluate the biocompatibility of materials is in an animal study. Using dogs as subjects, the purpose of this study was to evaluate the vestibular tissue reaction to cobalt chromium (Co-Cr), heat cure acrylic resin, and acrylic resin mixed with aluminum oxide (Al2O3) compared with a control group using the histopathologic method. METHODS AND MATERIALS: Twelve disk shape samples (2 mm x 8 mm) in four groups of Co-Cr, acrylic resin, acrylic resin mixed with a 20% weight ratio of Al2O3, and a control group (Teflon) were fabricated. In one stage surgery two samples of each material (8 samples) was implanted in the buccal vestibule of each dog (n=6), subcutaneously. At 45 and 90-day intervals, half of the samples were excised along with peripheral tissue to assess the presence of inflammation by grading on a scale from 0 to 3 and the presence of a fibrotic capsule using histological observations. Data were analyzed using the Kruskal-Wallis, Mann-Whitney, and Tau b Kendal tests. RESULTS: Tissue reaction between Co-Cr and the control group was significant (P=0.02), but it was not significant between other groups. There was no significant difference between the 45 and 90-day post-insertion samples. The formation of fibrotic capsule groups was significant (P=0.01). It was significant between the Co-Cr and acrylic resin groups (P=0.01) and the acrylic resin and control groups (P=0.01). CONCLUSION: The Co-Cr group was more toxic than the other groups. The inflammation increased during time. The inflammation in two acrylic groups was greater than the control and less than the Co-Cr group. The formation of fibrotic capsule, except in the acrylic resin with Al2O3 group, increased over time. CLINICAL SIGNIFICANCE: Co-Cr alloys are toxic and can produce damage to living tissue. Heat cure acrylic resin materials have less toxicity, and their use is safer than Co-Cr alloys.

Descriptors: biocompatible materials chemistry, dental materials chemistry, denture bases, acrylic resins chemistry, aluminum oxide chemistry, biocompatible materials toxicity, chromium alloys chemistry, chromium alloys toxicity, dental materials toxicity, dental polishing, dogs, fibroblasts pathology, fibrosis, lymphocytes pathology, macrophages pathology, materials testing, methylmethacrylates chemistry, models, animal, mouth mucosa pathology, neutrophils pathology, plasma cells pathology, polytetrafluoroethylene chemistry, random allocation, stomatitis pathology, surface properties, time factors.

Franco, R.L., R. Chiesa, P.T. de Oliveira, M.M. Beloti, and A.L. Rosa (2008). **Bone response to a Ca- and P-enriched titanium surface obtained by anodization.** *Brazilian Dental Journal* 19(1): 15-20.

Abstract: This study evaluated bone response to a Ca- and P- enriched titanium (Ti) surface treated by a multiphase anodic spark deposition coating (BSP-AK). Two mongrel dogs received bilateral implantation of 3 Ti cylinders (4.1 x 12 mm) in the humerus, being either BSP-AK treated or untreated (machined - control). At 8 weeks postimplantation, bone fragments containing the implants were harvested and processed for histologic and histomorphometric analyses. Bone formation was observed in cortical area and towards the medullary canal associated to approximately 1/3 of implant extension. In most cases, in the medullary area, collagen fiber bundles were detected adjacent and oriented parallel to Ti surfaces. Such connective tissue formation exhibited focal areas of mineralized matrix lined by active osteoblasts. The mean percentages of bone-to-implant contact were 2.3 (0.0-7.2 range) for BSP-AK and 0.4 (0.0-1.3 range) for control. Although the Mann-Whitney test did not detect statistically significant differences between groups, these results indicate a trend of BSP-AK treated surfaces to support contact osteogenesis in an experimental model that produces low bone-to-implant contact values.

Descriptors: calcium chemistry, coated materials, biocompatible chemistry, dental implants, dental materials chemistry, electroplating methods, humerus pathology, phosphorus chemistry, titanium chemistry, bone marrow pathology, bone remodeling physiology, collagen, connective tissue pathology, dental prosthesis design, dogs, electron probe microanalysis, humerus surgery, microscopy, electron, scanning, models, animal, osseointegration physiology, osteoblasts pathology, osteoclasts pathology, osteogenesis physiology, oxygen analysis, porosity, surface properties.

Freire, J.N., N.R. Silva, J.N. Gil, R.S. Magini, and P.G. Coelho (2007). **Histomorphologic and histomophometric evaluation of immediately and early loaded mini-implants for orthodontic anchorage.** *American Journal of Orthodontics and Dentofacial Orthopedics Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics* 131(6): 704.e1-9.

NAL Call Number: RK1

Abstract: INTRODUCTION: The purpose of this study was to evaluate the bone response to statically loaded 2.5-mm diameter mini-implants of 6 and 10 mm lengths activated after various healing periods in a dog model. METHODS: Seventy-eight machined-surface Ti-6Al-4V mini-implants were bilaterally placed in the mandibular premolar and molar regions of 6 beagle dogs. The left (experimental) and the right (control) hemi-arches received 6 and 7 mini-implants, respectively. Experimental mini-implants healing periods of 0 days

(immediately activated), 1 week, and 3 weeks were followed by a 12-week load activation period (250 g between parallel implant pairs). Control (nonloaded) mini-implant groups were placed for 12 weeks, 3 weeks, and 1 week before the dogs were killed they provided data concerning the experimental groups' bone to mini-implant scenarios at load activation times. The mandibles were exposed by sharp dissection, and decalcified specimens were prepared for histomorphologic and histomorphometric (bone to mini-implant contact) assessment. RESULTS: Survival rates were 100% and 77.78% for the control and the experimental groups, respectively. Survival rates were 88.89% for the 10-mm and 66.67% for the 6-mm experimental groups. All failed devices had tissue inflammation and were lost after spring placement. The control groups showed classic bone-healing events, and the experimental groups showed mature bone morphology after 12 weeks in vivo regardless of placement time before load activation. Bone to implant contact values were not significantly different between the experimental and the control groups that remained 12 weeks in vivo. CONCLUSIONS: These results showed that low-intensity immediate or early orthodontic static loads did not affect mini-implant performance.

Descriptors: dental implants adverse effects, dental stress analysis, orthodontic anchorage procedures instrumentation, osseointegration, analysis of variance, dental alloys, dental implantation, endosseous adverse effects, dental prosthesis design, dogs, mandible surgery, miniaturization, models, animal, orthodontic anchorage procedures adverse effects, periodontitis etiology, time factors, titanium, wound healing.

He, Y., Z.Y. Zhang, H.G. Zhu, W. Qiu, X. Jiang, and W. Guo (2007). **Experimental study on reconstruction of segmental mandible defects using tissue engineered bone combined bone marrow stromal cells with three-dimensional tricalcium phosphate.** *Journal of Craniofacial Surgery* 18(4): 800-5. ISSN: 1049-2275.

Abstract: Reconstructive procedures of segmental mandible defects often require bone graft harvesting, which results in donor site morbidity; the use of tissue-engineered bone might mitigate this problem. The aim of the present experimental pilot study was to produce three-dimensional (3D) autologous tissue-engineered constructs that combine autogenous cultivated bone marrow stromal cells with beta-tricalcium phosphate to reconstruct segmental mandible defects without donor site morbidity. Bone marrow stromal cells were isolated from a dog's caput femoris. After differentiation and proliferation in vitro, the cells were seeded into a 3D beta-tricalcium phosphate scaffold. The constructs were incubated under osteogenic culture conditions for 5 days. Segmental defects of 30 mm length were created unilaterally in the mandibles of the animals. Reconstruction was performed using the construct in three dogs and the scaffold only in three dogs as a control group. The specimens were retrieved 3 months later, and the reconstructed areas were processed for gross observation, radiographic examination, 3D computed tomographic (CT) imaging, biomechanical evaluations, and histologic observation. The construct implanted group ($n = 3$) showed an average height of the reconstructed area of 18.54 mm and the control group 9.16 mm ($P < 0.05$). Higher radiodensity was present in the construct group than in the control group, as shown by radiograph. 3D CT imaging showed nearly two-thirds absorption of the reconstructed area in the control group. The biomechanical examination of the construct and control groups showed a compression strength of 102.77 N and 42.90 N and stress of 3.504 N/mm and 1.930 N/mm, which demonstrates significant difference. Histologic micrographs

showed new bone formation in the scaffolds in central sections of the defects in the construct group 3 months later, with osteoblast seams, osteoclastic resorption, and cartilage formation. The construct of morphologic, 3D beta-tricalcium phosphate scaffold seeded, autologous bone marrow stromal cells ensure bone formation and vascularization throughout the procedure of mandible segmental defect reconstruction, closely resembling how tissue engineering would be used to reconstruct a segmental mandible defect in the clinical setting.
Descriptors: bone substitutes chemistry, calcium phosphates chemistry, mandible surgery, oral surgical procedures methods, tissue engineering methods, dogs, mandible cytology, models, animal, pilot projects, stromal cells.

Lee, H.J., B.H. Choi, J.H. Jung, S.J. Zhu, S.H. Lee, J.Y. Huh, T.M. You, and J. Li (2007). **Maxillary sinus floor augmentation using autogenous bone grafts and platelet-enriched fibrin glue with simultaneous implant placement.** *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 103(3): 329-33.
Abstract: OBJECTIVE: The aim of this study was to evaluate the use of autogenous bone in combination with platelet-enriched fibrin glue as a grafting material for maxillary sinus augmentation with simultaneous implant placement in dogs. STUDY DESIGN: The mucous membranes of 12 sinuses in 6 dogs were elevated bilaterally. In the right sinus, autogenous bone mixed with platelet-enriched fibrin glue was grafted into the space between the membrane and the sinus wall. In the left sinus, autogenous bone alone was grafted as a control. At the same time, 2 dental implants were inserted into the grafting material through the maxillary sinus floor. The animals were killed 6 months after surgery. RESULTS: The mean bone-implant contact was 40.5% on the fibrin glue side and 32.3% on the control side ($P < .05$). The mean height of newly formed bone in the augmented area was 12.2 mm on the fibrin glue side and 10.7 mm on the control side ($P < .05$). CONCLUSION: The results indicate that the use of autogenous bone mixed with platelet-enriched fibrin glue can achieve results superior to those for grafts of autogenous bone alone. The specific improvements of this technique include enhanced osseointegration of dental implants and increased height of new bone.
Descriptors: bone regeneration drug effects, bone transplantation methods, dental implantation, endosseous, fibrin tissue adhesive pharmacology, maxillary sinus surgery, oral surgical procedures, preprosthetic methods, platelet rich plasma, dogs, models, animal, statistics, nonparametric.

Marin, C., R. Granato, M. Suzuki, J.N. Gil, A. Piattelli, and P.G. Coelho (2008). **Removal torque and histomorphometric evaluation of bioceramic grit-blasted/acid-etched and dual acid-etched implant surfaces: an experimental study in dogs.** *Journal of Periodontology* 79(10): 1942-9. ISSN: 0022-3492.
Abstract: BACKGROUND: Surface modifications to dental implants have been used in an attempt to accelerate the osseointegration process. The objective of this study was to biomechanically/histomorphometrically evaluate a bioceramic grit-blasted and acid-etched surface (BGB/AA; test) versus a dual acid-etched implant surface (control) in a beagle dog model. METHODS: Control and BGB/AA implants were subjected to a series of physicochemical characterization tools, including scanning electron microscopy (SEM), atomic force microscopy (AFM), and auger photoelectron spectroscopy (APS). The animal model included

the placement of 72 implants along the proximal tibiae of six beagle dogs, which remained in place for 2 or 4 weeks. After euthanization, half of the specimens were biomechanically tested (removal torque), and the other half was non-decalcified processed to slides of approximately 30 microm thickness for histomorphologic and histomorphometric (percentage of bone-to-implant contact [%BIC]) evaluation. Analysis of variance at the 95% confidence level and the Tukey post hoc test were used for multiple comparisons. RESULTS: SEM and AFM showed that surface microtextures were qualitatively and quantitatively different and that the BGB/AA surface presented higher submicrometer average roughness values (R(a)) and root mean square (RMS) values compared to control surfaces. Ca and P were detected at the BGB/AA surface by APS. Higher degrees of bone organization were observed along the perimeter of the BGB/AA surface compared to control, despite the non-significant differences in %BIC between the surfaces (P >0.25). Significantly higher removal torque was observed for the BGB/AA implants at both time periods (P <0.0001). CONCLUSION: According to the biomechanical and histomorphologic results, early biomechanical fixation was positively affected by the BGB/AA surface compared to the dual-acid etched surface.
Descriptors: acid etching, dental methods, biocompatible materials chemistry, ceramics chemistry, dental etching methods, dental implants, torque, biomechanics, bone remodeling physiology, calcium analysis, carbon analysis, dental prosthesis design, dogs, electron probe microanalysis, materials testing, microscopy, atomic force, microscopy, electron, scanning, models, animal, osseointegration physiology, oxygen analysis, phosphorus analysis, surface properties, tibia pathology, tibia surgery, titanium analysis.

Nethander, G., A. Skoglund, and K.E. Kahnberg (2003). **Experimental autogenous tooth transplantation in the dog: a comparison between one- and two-stage surgical techniques.** *Acta Odontologica Scandinavica* 61(4): 223-229. ISSN: 0001-6357.
Abstract: Crucial if tooth transplantation is to succeed is preservation of the vitality of the cells of the periodontium and cementum of the tooth graft. Poor contact between the tissues of the recipient site and the root surface when teeth are transplanted to recipient sites prepared immediately prior to transplantation (one-stage technique) could, after transplantation, result in insufficient nutrition to the cells of the root surface and contribute to necrosis of the cells. To improve nutrition, tooth transplantation to recipient beds left to heal for 14 days was performed (two-stage technique). Clinical trials of tooth transplantation by the two-stage technique resulted in a low incidence of tooth graft loss and root resorption. The different results between these two methods, as well as difficulties in evaluating clinical trials, called for an experimental model to be established. In 5 beagle dogs, fully developed autogenous teeth were transplanted using both one-stage and two-stage surgical techniques. The control teeth were transplanted by the one-stage method to recipient beds prepared immediately before transplantation. The test teeth were transplanted using the two-stage method to recipient beds prepared and left to heal for 5 days prior to transplantation. Four pairs of teeth (1 test and 1 control) were transplanted in each dog. One pair of incisors and one pair of premolars were transplanted in the maxilla and in the mandible. Altogether 20 pairs of teeth were included in the study. One pair of teeth fractured during extraction and was therefore excluded from the study. Two pairs of teeth were lost in the first hours after transplantation. Evaluation of the remaining 17 pairs of teeth was made by routine histological examinations after a 6-month period of healing. The blinded examination failed to show a difference

between the two surgical methods in terms of frequency of various types of root resorption. The differences between the results after long-term observation of human teeth transplanted by the one- and two-stage tooth transplantation techniques were not found by this experimental model.
Descriptors: cell biology, dental and oral system, ingestion and assimilation, methods and techniques, root resorption, dental and oral disease, autogenous tooth transplantation, experimental surgical techniques, laboratory techniques, histology, histology and cytology techniques, laboratory techniques, one stage surgical treatment, two stage surgical treatment, experimental surgical techniques, laboratory techniques, cell nutrition, cell vitality, clinical trials, disease frequency, experimental model, necrosis, recipient site, technique comparison, tissue contact, tooth graft loss, wound healing.

Novaes, A.B.J., A.M. Marcaccini, S.L. Souza, M.J. Taba, and M.F. Grisi (2003). **Immediate placement of implants into periodontally infected sites in dogs: a histomorphometric study of bone-implant contact.** *The International Journal of Oral and Maxillofacial Implants* 18(3): 391-8. ISSN: 0882-2786.
Abstract: PURPOSE: The placement of implants allows for re-establishment of function and esthetics following tooth loss. Immediate implant placement is a relatively recent procedure and has advantages, such as reduced number of surgical procedures, preservation of alveolar bone, reduction of cost and period of edentulism, and increased patient acceptance. However, there are some specific contraindications for the technique, such as the presence of an infection caused by periodontal disease and periapical lesions. The objective of this study was to evaluate the percentage of bone-implant contact of immediate implants placed in periodontally infected sites. MATERIALS AND METHODS: In the first phase, periodontitis was induced with ligatures in the mandibular premolars of 5 mongrel dogs, using the contralateral teeth as controls (received prophylaxis only). After 3 months, in the second phase of the study, 40 implants were placed in the alveoli of both experimental and control teeth. After a healing period of 12 weeks, the animals were euthanized, and the hemimandibles were removed, dissected, fixed, and prepared for histomorphometric analysis of percentage of bone-implant contact. The Mann-Whitney test was used for statistical analysis. RESULTS: The results of the histomorphometric analysis indicated mean bone-implant contact of 62.4% in the control group and 66.0% in the experimental group, a difference that was not statistically significant. DISCUSSION: Histomorphometric results revealed similar bone-implant contact in both groups, with no signs of infection. CONCLUSIONS: It was concluded that periodontally infected sites may not be a contraindication for immediate implantation in this animal model system, if adequate pre- and postoperative care is taken.
Descriptors: animal model, implants, tooth loss, alveolar bone, pre and postoperative care.

Pearce, A.I., R.G. Richards, S. Milz, E. Schneider, and S.G. Pearce (2007). **Animal models for implant biomaterial research in bone: a review.** *European Cells and Materials* 13: 1-10.
NAL Call Number: R857.M3 E97
Abstract: Development of an optimal interface between bone and orthopaedic and dental implants has taken place for many years. In order to determine whether a newly developed implant material conforms to the requirements of biocompatibility, mechanical stability and safety, it must undergo rigorous testing both in vitro and in vivo. Results from in vitro

studies can be difficult to extrapolate to the in vivo situation. For this reason the use of animal models is often an essential step in the testing of orthopaedic and dental implants prior to clinical use in humans. This review discusses some of the more commonly available and frequently used animal models such as the dog, sheep, goat, pig and rabbit models for the evaluation of bone-implant interactions. Factors for consideration when choosing an animal model and implant design are discussed. Various bone specific features are discussed including the usage of the species, bone macrostructure and microstructure and bone composition and remodelling, with emphasis being placed on the similarity between the animal model and the human clinical situation. While the rabbit was the most commonly used of the species discussed in this review, it is clear that this species showed the least similarities to human bone. There were only minor differences in bone composition between the various species and humans. The pig demonstrated a good likeness with human bone however difficulties may be encountered in relation to their size and ease of handling. In this respect the dog and sheep/goat show more promise as animal models for the testing of bone implant materials. While no species fulfils all of the requirements of an ideal model, an understanding of the differences in bone architecture and remodelling between the species is likely to assist in the selection of a suitable species for a defined research question.
Descriptors: bone substitutes, implants, experimental, materials testing, models, animal, bone remodeling, bone and bones anatomy and histology, dogs, goats anatomy and histology, rabbits, sheep anatomy and histology, swine anatomy and histology.

Ren, A., T. Lv, N. Kang, B. Zhao, Y. Chen, and D. Bai (2007). **Rapid orthodontic tooth movement aided by alveolar surgery in beagles.** *American Journal of Orthodontics and Dentofacial Orthopedics Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics* 131(2): 160.e1-10.
Abstract: INTRODUCTION: It has been reported that oral surgery can accelerate orthodontic tooth movement. The purpose of this study was to evaluate the effects of alveolar surgery that undermines interseptal bone in orthodontic tooth movement. METHODS: Ten male beagles, aged 12 to 15 months, were used in this study. Extraction of the mandibular second premolar and alveolar surgery to reduce the osteal resistance on the mesial side of the extraction socket were performed on the experimental side; on the control side, only the second premolar was extracted. The first premolars were distalized against the third premolars with orthodontic nickel-titanium coil springs on the both sides. The beagles were killed in the first, second, third, fourth, and eighth weeks after orthodontic force application. RESULTS: The first premolar on the experimental side moved more rapidly than that on the control side ($P < .01$). Tissue slices were obtained for histological evaluation. No obvious root resorption and no irreversible injury to the pulp were observed on either side. Active and extensive bone resorption in the compressive area and bone deposition in the tension area were observed on the experimental sides. CONCLUSIONS: Self-fluorescence checks showed that more new bone was deposited in the tension area of the experimental side than on the control side ($P < .05$). These results suggest that alveolar surgery might be an effective and safe way to aid orthodontic tooth movement.
Descriptors: bicuspid surgery, molar, tooth movement methods, tooth socket surgery, bicuspid radiography, bone regeneration physiology, dogs, fluorescence, models, animal, root resorption radiography, time factors, tooth extraction, tooth socket metabolism.

Saito, E., A. Saito, and M. Kawanami (2003). **Favorable healing following space creation in rhbmp-2-induced periodontal regeneration of horizontal circumferential defects in dogs with experimental periodontitis.** *Journal of Periodontology* 74(12): 1808-1815. ISSN: 0022-3492.

Abstract: Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is believed to be capable of inducing periodontal regeneration. However, the risk of aberrant healing events, such as root resorption and ankylosis, has been reported. We hypothesized that implantation of BMP-containing carriers directly on the root planed surface may be the cause of unfavorable healing. The purpose of this study was to evaluate the influence of a 1 mm spacer membrane, which separated the rhBMP-2 in polymer-coated gelatin sponge (PGS) and the root surface, on periodontal regeneration of experimentally induced horizontal defects in dogs. Methods: Horizontal circumferential periodontal defects were surgically created, and experimental periodontitis was induced in 72 maxillary and mandibular premolars of four male beagle dogs. The recipient sites of each quadrant received: 1) rhBMP-2/PGS (B group) (rhBMP-2 at 1.0 mg/ml, total implant volume/site apprx7.2 mul) (n=24); 2) rhBMP-2/PGS with a spacer membrane (PB group) (n=24); and 3) physiological saline (PS)/PGS as a control (P group) (n=24). One quadrant was left untreated. Dogs were sacrificed at 12 weeks post-surgery, and healing was evaluated histologically. Results: Both groups treated with rhBMP-2/PGS demonstrated enhanced new bone formation and connective tissue attachment with cementum regeneration when compared to the control group. Sites treated with rhBMP-2/PGS showed a greater degree of bone formation than sites treated with rhBMP-2/PGS and spacer membrane, although the latter sites showed no ankylosis. Conclusions: Implantation of rhBMP-2/PGS enhances bone formation and connective tissue attachment in horizontal circumferential defects. In addition, the use of a spacer membrane reduces the degree of bone formation, but minimizes ankylosis.

Descriptors: biochemistry and molecular biophysics, dental and oral system, ingestion and assimilation, skeletal system, movement and support, periodontitis, dental and oral disease, diagnosis, therapy, horizontal circumferential defect, periodontal regeneration, wound healing.

Schliephake, H., D. Scharnweber, M. Dard, S. Roessler, A. Sewing, and C. Huettmann (2003). **Biological performance of biomimetic calcium phosphate coating of titanium implants in the dog mandible.** *Journal of Biomedical Materials Research* 64A(2): 225-234. ISSN: 0021-9304.

NAL Call Number: R856.J6

Abstract: The aim of the present study was to analyze the in vivo effect of biomimetic calcium phosphate coating of titanium implants on periimplant bone formation and bone-/implant contact. Five types of implants were used: 1) Ti6Al4V implants with a polished surface; 2) Ti6Al4V implants with collagen coating; 3) Ti6Al4V implants with a mineralized collagen layer; 4) Ti6Al4V implants with sequential coating of hydroxyapatite (HA) and collagen; and 5) Ti6Al4V implants with HA coating only. All implants had square cross sections with an oblique diameter of 4.6 mm and were inserted press fit into trephine burr holes of 4.6 mm in the mandibles of ten beagle dogs. The implants of five animals each were evaluated after a healing period of 1 month and 3 months, respectively, during which time sequential fluorochrome labeling of bone formation had been performed. Bone formation

was evaluated by morphometric measurement of the newly formed bone around the implants and the percentage of implant bone contact. After 1 month, there was a significantly higher percentage of mean bone/implant contact in the HA-coated implants compared to those with polished surface and those with the collagen-coated surface. After 3 months, these differences were not present anymore. Bone apposition was significantly higher next to implants with sequential HA/collagen coating compared to polished surfaces and mineralized collagen layer. It is concluded that biomimetic coating of titanium implants with HA has shown the clearest trend to increase bone-implant contact in the early ingrowth period. The addition of collagen to an HA coating layer may hold some promise when used as sequential HA/collagen coating with mineralized collagen as the surface layer.
Descriptors: biomaterials, dental and oral system, ingestion and assimilation, skeletal system, movement and support, titanium implant, medical equipment, bone formation, cell adhesion, osseointegration, periimplant bone formation.

Shi, B., Y. Zhou, Y.N. Wang, and X.R. Cheng (2007). **Alveolar ridge preservation prior to implant placement with surgical-grade calcium sulfate and platelet-rich plasma: a pilot study in a canine model.** *International Journal of Oral and Maxillofacial Implants* 22(4): 656-65. ISSN: 0882-2786.
Abstract: PURPOSE: To evaluate the combination of surgical-grade calcium sulfate (SGCS) and platelet-rich plasma (PRP) for alveolar ridge preservation prior to implant placement. MATERIALS AND METHODS: Five mongrel dogs were used as subjects. Four enlarged mandibular extraction sockets, 2 on each side, were created in each dog. According to a split-mouth design, the 2 anterior sockets received either SGCS/PRP (SGCS/PRPant) or were left unfilled, while the 2 posterior sockets received either SGCS/PRP (SGCS/PRPpost) or SGCS. Computerized tomographic (CT) scans were conducted at 1 day and 8 weeks postextraction to detect the change in ridge height. Bone scintigraphy was performed at 2, 4, and 6 weeks to investigate new bone formation activity. At 8 weeks, 1 dog was sacrificed for histologic and histomorphometric study. Meanwhile, implants were placed in the remaining 4 dogs. These 4 dogs were sacrificed after 3 months. RESULTS: Less ridge resorption was observed in the anterior SGCS/PRP-filled sites compared to unfilled sites (P = .001), while no significant difference was found between the SGCS/PRPpost and SGCS groups (P = .544). Bone scintigraphy showed that sites filled with SGCS/PRP showed significantly higher count/pixel at 2 (P = .028), 4 (P = .009), and 6 weeks (P = .037) than the unfilled sites. Nevertheless, the SGCS/PRPpost group achieved significantly higher values than the SGSC group only at 2 weeks (P = .036). Histomorphometrically, the SGCS/PRPant group showed a significantly higher percentage of bone-implant contact than the unfilled group (P = .024), but no significant difference was detected between the SGCS/PRPpost and SGCS groups (P = .979). CONCLUSION: Grafting SGCS/PRP in fresh extraction sockets reduced alveolar ridge resorption and promoted the bone formation in this canine model. The addition of PRP to SGCS resulted in the enhancement of bone regeneration in the early phase of healing.
Descriptors: alveolar process surgery, bone substitutes therapeutic use, calcium sulfate therapeutic use, dental implants, mandible surgery, platelet rich plasma, alveolar bone loss prevention and control, alveolar process pathology, bone regeneration physiology, bone resorption prevention and control, dogs, mandible pathology, models, animal, osseointegration physiology, osteogenesis physiology, pilot projects, radiopharmaceuticals diagnostic use,

technetium tc 99m medronate diagnostic use, time factors, tomography, x ray computed, tooth extraction, tooth socket pathology, tooth socket surgery.

Sperandio, C.B., L.F. Silveira, L.A. de Araujo, J. Martos, and A. Malshe (2008). **Response of the periapical tissue of dogs' teeth to the action of citric acid and EDTA.** *Journal of Applied Oral Science Revista FOB* 16(1): 59-63.

Abstract: The purpose of this study was to analyze the inflammatory response of dog's periapical tissues to 17% trisodium EDTA salt (pH 8.0) and 1% citric acid (pH 2.0). Saline was used as a control. Six adult dogs were used as the biological model of the study. The experimental units comprised 56 roots of mandibular molars (first and second) and premolars (first, second and third). After coronal opening, pulpectomy and root canal instrumentation were performed using the above-mentioned irrigating solutions. After 24 and 48 hours, the animals were euthanized and the teeth and their supporting tissues were removed and histologically processed. The sections were stained with hematoxylin and eosin and analyzed histopathologically with a light microscope at x100 magnification. The histological analysis focused on the occurrence of acute inflammatory response. The presence of swelling, vasodilatation and inflammatory cells were evaluated and the degree of inflammation was determined for each case. Data were analyzed by Fisher's exact test using the SPSS software with a confidence interval of 95% ($p<0.05$). 17% EDTA and 1% citric acid caused inflammatory responses in dog's periapical tissues with no significant differences to each other or to saline (control) at either the 24-hour ($p=0.482$) or 48-hour ($p=0.377$) periods. It may be concluded that the inflammatory response was of mild intensity for the tested substances.

Descriptors: biocompatible materials therapeutic use, citric acid therapeutic use, edetic acid therapeutic use, periapical tissue drug effects, root canal irrigants therapeutic use, bicuspid pathology, dogs, edema chemically induced, edema pathology, models, animal, molar pathology, periapical periodontitis chemically induced, periapical periodontitis pathology, periapical tissue pathology, pulpectomy methods, root canal preparation instrumentation, root canal preparation methods, time factors, vasodilation drug effects.

Tomofuji, T., D. Ekuni, T. Yamamoto, M. Horiuchi, T. Sakamoto, and T. Watanabe (2003). **Optimum force and duration of toothbrushing to enhance gingival fibroblast proliferation and procollagen type i synthesis in dogs.** *Journal of Periodontology* 74(5): 630-634. ISSN: 0022-3492.

Abstract: Background: Toothbrushing enhances gingival fibroblast proliferation, which promotes wound healing. Optimum force and duration of toothbrushing for stimulation of fibroblast proliferation are key factors in maximizing effects of toothbrushing on periodontal wound healing. We therefore evaluated the effects of different durations and forces of toothbrushing on proliferative activity and procollagen synthesis of gingival fibroblasts. Methods: Twelve dogs were used. In each dog, buccal gingivae of 12 teeth were examined for 3 weeks. Nine of these 12 teeth were each assigned to 1 of 9 different combinations of brushing force (0.98, 1.96, or 2.45 N) and duration (10, 20, or 40 seconds). The remaining 3 teeth received plaque removal without brushing, via a scaler. Results: Force and duration of toothbrushing affected both proliferating cell nuclear antigen (PCNA)-positive and procollagen Type I C-peptide (PIP)-positive fibroblast ratios ($P<0.05$). The highest ratio of PCNA-positive fibroblasts was produced by brushing at 1.96 N for 20 seconds. The highest ratio of PIP-positive

fibroblasts was produced by brushing at 1.96 N for 10 seconds. Conclusions: Toothbrushing at certain forces and durations enhanced the proliferative activity and procollagen synthesis of gingival fibroblasts. The toothbrushing duration that increased procollagen synthesis (10 seconds) was shorter than that which increased fibroblast proliferative activity (20 seconds).
Descriptors: dental and oral system, ingestion and assimilation, methods and techniques, periodontal wound healing, toothbrushing, optimum force, duration.

Toomarian, L., R. Fekrazad, D. Sharifi, M. Baghaei, H. Rahimi, and B. Eslami (2008). **Histopathological evaluation of pulpotomy with Er,Cr:YSGG laser vs formocresol.** *Lasers in Medical Science* 23(4): 443-50. ISSN: 0268-8921.
Abstract: The purpose of this study was to histologically investigate whether pulpotomy with Er,Cr:YSGG laser is an acceptable alternative for formocresol. Pulpotomy of 48 dog's primary canine teeth was performed with formocresol or Er,Cr:YSGG laser. Histological evaluations on hematoxylin and eosin-stained pulp tissues were made by an optical microscope 7 or 60 days later. Statistical analysis was performed with Fisher's exact test, Mann-Whitney U test, and Student's t test. Seven days after pulpotomy, samples treated with laser had significantly favorable histological features in the following measures: continuity of odontoblastic layer ($P<0.001$), presence of hemorrhage ($P<0.008$), amount of inflammation ($P<0.002$), tissue necrosis ($P<0.001$), internal resorption ($P<0.002$), level of vascularization ($P<0.002$), and size of abscess ($P<0.041$). Similar results were observed 60 days after pulpotomy, except that the differences were not mostly significant due to natural exfoliation of 16 teeth. In conclusion, Er,Cr:YSGG laser system is an acceptable alternative for formocresol in pulpotomy of deciduous teeth.
Descriptors: dental pulp radiation effects, formocresols therapeutic use, hematoxylin radiation effects, laser therapy instrumentation, lasers, solid state, pulpotomy instrumentation, tooth, deciduous radiation effects, dental pulp drug effects, dogs, laser therapy methods, models, animal, odontoblasts radiation effects, pilot projects, pulpotomy methods, zinc oxide.

van Leeuwen, E.J., J.C. Maltha, A.M. Kuijpers Jagtman, and M.A. Van't Hof (2003). **The effect of retention on orthodontic relapse after the use of small continuous or discontinuous forces. An experimental study in beagle dogs.** *European Journal of Oral Sciences* 111(2): 111-116. ISSN: 0909-8836.
Abstract: Relapse is a major concern in orthodontics for which avoidance retention is the general procedure. However, the effect of retention on relapse after active tooth movement with different force regimes has never been studied in a standardized experimental setting. Mandibular third premolars were extracted in 19 young adult beagle dogs. Three months later, the second premolars were bodily moved distally with forces of 10 cN or 25 cN. The forces were applied for 24 h d-1 or for 16 h d-1. After 4 months, relapse was allowed in half of the animals, while in the others relapse was preceded by retention for 90 d. Statistical analyses were performed on the relation between force regime, active tooth movement, retention, and relapse. Force magnitude had no effect on relapse, while continuous forces resulted in a longer-lasting and more pronounced relapse than did discontinuous forces. A significant positive correlation was found between the amount of active tooth movement and both the rate and the total amount of relapse, but not between the amount of active tooth movement

and the duration of the relapse. Retention had no effect on the duration of the relapse, but it strongly decreased its total amount. Finally, the effect of retention on the amount of relapse was strongly correlated with the amount of active tooth movement.
Descriptors: dental and oral system, ingestion and assimilation, equipment apparatus devices and instrumentation, orthodontic appliance, prosthetic, continuous forces, discontinuous forces, orthodontic relapse, retention.

Yamauchi, K., T. Takahashi, K. Funaki, and Y. Yamashita (2008). **Periosteal expansion osteogenesis using highly purified beta-tricalcium phosphate blocks: a pilot study in dogs.** *Journal of Periodontology* 79(6): 999-1005. ISSN: 0022-3492.
Abstract: BACKGROUND: In highly atrophic edentulous jaws, the augmentation of the alveolar process is standard treatment for dental implantation because of the lack of alveolar bone height and width. Our aim was to examine periosteal expansion osteogenesis in a dog model, based on the concept of distraction osteogenesis, using a highly purified beta-tricalcium phosphate (beta-TCP) block instead of an original bone segment. METHODS: Three beagle dogs weighing 10 to 12 kg were used. The beta-TCP block was placed at the lateral surface of the mandibular bone. Two titanium screws were inserted from the lingual aspect to push the block to the buccal side. After a latency period of 8 days, during which primary wound healing occurred, the lingual screws were advanced by approximately 0.5 mm/day for 8 days. Specimens were taken 8 weeks after lingual screw adjustments ceased and were analyzed by hematoxylin and eosin, tartrate-resistant acid phosphatase (TRAP), and Villanueva bone staining. RESULTS: The alveolar form at the experimental region was changed dramatically following lateral expansion with the beta-TCP block. Newly formed bone was observed in the gap between the bone and the beta-TCP block, as well as on the lateral surface of the block. Moreover, the replacement of large parts of beta-TCP with newly formed bone was observed in the beta-TCP block area. However, newly formed bone was not observed over the upper parts of the block, and multinucleated TRAP-positive cells were attached to the beta-TCP in the periphery of this area. CONCLUSION: The highly purified beta-TCP block worked as an activator for the soft tissue, including the periosteum, as well as a space maker to induce an osteoblastic response in the periosteum.
Descriptors: alveolar ridge augmentation methods, bone substitutes, calcium phosphates, osteogenesis, distraction methods, periosteum physiology, dogs, models, animal, osteogenesis, pilot projects.

You, T.M., B.H. Choi, J. Li, F. Xuan, S.M. Jeong, and S.O. Jang (2009). **Morphogenesis of the peri-implant mucosa: a comparison between flap and flapless procedures in the canine mandible.** *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 107(1): 66-70.
Abstract: OBJECTIVE: Although it has been shown that the exclusion of the mucoperiosteal flap can prevent postoperative bone resorption associated with flap elevation, there have been only a few studies on the peri-implant mucosa following flapless implant surgery. The purpose of this study was to compare the morphogenesis of the peri-implant mucosa between flap and flapless implant surgeries by using a canine mandible model. STUDY DESIGN: In six mongrel dogs, bilateral edentulated flat alveolar ridges were created in the mandible. After 3 months of healing, 2 implants were placed in each side by either the flap

or the flapless procedure. Three months after implant insertion, the peri-implant mucosa was evaluated by using clinical, radiologic, and histometric parameters, which included the gingival index, bleeding on probing, probing pocket depth, marginal bone loss, and the vertical dimension of the peri-implant tissues. RESULTS: The height of the mucosa, length of the junctional epithelium, gingival index, bleeding on probing, probing depth, and marginal bone loss were all significantly greater in the dogs that had the flap procedure than in those that had the flapless procedure ($P < .05$). CONCLUSION: These results indicate that gingival inflammation, the height of junctional epithelium, and bone loss around nonsubmerged implants can be reduced when implants are placed without flap elevation.
Descriptors: dental implantation, endosseous methods, epithelial attachment physiology, mouth mucosa physiology, alveolar bone loss etiology, dental implantation, endosseous adverse effects, dental implants, dogs, epithelial attachment pathology, epithelial attachment surgery, gingivitis etiology, implants, experimental, mandible surgery, models, animal, morphogenesis, mouth mucosa pathology, mouth mucosa surgery, periodontal index, random allocation.

Zhou, H.Z., M. Hu, H.C. Liu, J. Yao, M. Xie, and H.X. Xiao (2003). **[Reconstruction of segmental mandibular defect of canine using titanium-nickel distractor]**. *Zhonghua Kou Qiang Yi Xue Za Zhi.* 38(5): 333-5. ISSN: 1002-0098.
Abstract: OBJECTIVE: To establish a continuous and automatic distraction osteogenesis technique in reconstruction of segmental mandibular defect by using embedded titanium-nickel alloy distractor with characteristics of shape-memory and super-elasticity. METHODS: Adult hybrid canines were used as the animal model. Segmental defects of 1-3 cm in the body of mandible were created by surgical osteotomy. Bi-focal distraction osteogenesis was applied using embedded titanium-nickel distractor designed by the authors. The canines were sacrificed 3 months after the operation and the mandibles were harvested to examine the results of bone regeneration. RESULTS: The histocompatibility of titanium-nickel distractors was good. Distraction osteogenesis was completed automatically and the defects were elementarily restored. Radiological and histological examination showed well bone regeneration in distraction area. CONCLUSIONS: Distraction osteogenesis using embedded self-loading titanium-nickel distractor could be a hopeful and useful technique. It might help to solve the problems of functional mandibular reconstruction in the near future.
Descriptors: animal model, segmental mandibular defect, surgical osteotomy, osteogenesis technique, reconstruction, methods, titanium-nickel alloy distractor, super-elasticity.

Digestive System

Buscaglia, J.M. (2007). **Animal laboratory endoscopic research: a fellow's perspective.** *Gastrointestinal Endoscopy* 65(6): 882-3. ISSN: 0016-5107.
Descriptors: animal experimentation, endoscopy, dogs, models, animal, swine.

Chaves, N.J., L.T. Magalhaes, R. Colleoni, and J.C. Del Grande (2007). **Effects of increased intra-abdominal pressure on the healing process after surgical stapling of the stomach of dogs.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(5): 379-86. ISSN: 0102-8650.
Abstract: PURPOSE: To assess the initial healing after surgical stapling of the stomach using a linear cutting stapler and creating pneumoperitoneum (12-14 mmHg) for 60 minutes or 120 minutes, and compare it with the healing of a staple line not submitted to increased pressure. METHODS: A total of 30 dogs were divided into three groups of 10 animals each: Group I (control group - surgical stapling), Group II (surgical stapling and increased intra-abdominal pressure for 60 minutes) and Group III (surgical stapling and increased intra-abdominal pressure for 120 minutes). All dogs were maintained under general anesthesia for two hours after surgical stapling. Seven days after surgery, the area around the staple line was macroscopically and microscopically examined. RESULTS: The macroscopic examination of the samples (n = 30) did not show dehiscence, fistula or abscess. Adhesions between the omentum and the staple line were observed in all animals of Groups II and III (n = 20), which were significantly different from Group I (p = 0.008*). The histopathological analysis showed normal healing up to day 7 in the control animals (n = 10). When these results were compared with those of Groups II and III (n = 20), non-parametric tests revealed that there was a significant difference with regard to certain parameters of the early stages of healing, such as fibroblast migration (p = 0.011*), edema (p < 0.001*) and congestion (p = 0.011*). These alterations affected reepithelization (p < 0.001*), and consequently the late stages of healing. CONCLUSIONS: Each group showed different healing stages, and the healing process was delayed in the groups submitted to increased pressure, especially in the group submitted to increased pressure for longer time.
Descriptors: abdomen physiopathology, pneumoperitoneum, artificial methods, stomach surgery, surgical stapling, wound healing physiology, carbon dioxide administration and dosage, cell proliferation, dogs, edema pathology, models, animal, pressure, stomach pathology, time factors, tissue adhesions pathology, wound healing drug effects.

Clarke, J.O., S.B. Jagannath, A.N. Kalloo, V.R. Long, D.M. Beitler, and S.V. Kantsevoy (2007). **An endoscopically implantable device stimulates the lower esophageal sphincter on demand by remote control: a study using a canine model.** *Endoscopy* 39(1): 72-6. ISSN: 0013-726X.
Abstract: BACKGROUND AND STUDY AIMS: Implantable microstimulators (IMS) have been used in a variety of medical conditions. Selective stimulation to increase lower esophageal sphincter (LES) pressure may be useful in the control of gastroesophageal reflux

disease. We evaluated on-demand stimulation of the LES with an endoscopically implanted microstimulator. MATERIALS AND METHODS: We performed acute experiments in three 30-kg dogs. After LES manometry, a 3.3 mm x 28 mm microstimulator (the Bion) was implanted into the LES. Manometry was repeated with and without IMS stimulation to record the changes in LES pressure. Stimulation amplitude was varied from 3 mA to 10 mA, with a fixed frequency of 20 Hz and a pulse width of 200 microsec. RESULTS: The mean LES pressures prior to IMS implantation in the three dogs were 13.0 mm Hg, 5.0 mm Hg, and 14.9 mm Hg. The mean pressures were not significantly changed by IMS placement. There were no documented changes in LES pressure when the amplitude of stimulation was less than 8 mA. After stimulation of the IMS at a setting of 10 mA in dogs 1 and 2 and at 8mA in dog 3, however, the resultant LES pressures were 62.1 mm Hg, 35.1 mm Hg, and 26.8 mm Hg respectively, more than three times higher than post-implantation baseline levels ($P < 0.02$). CONCLUSIONS: The LES pressure can be increased using an on-demand microstimulator. The implantation procedure is minimally invasive, represents a novel therapeutic approach to gastroesophageal reflux disease, and may have therapeutic potential for other gastrointestinal motility disorders.

Descriptors: electric stimulation therapy, electrodes, implanted, esophageal sphincter, lower physiology, robotics, dogs, esophagoscopy, manometry, models, animal, prosthesis implantation.

Dong, M.S., Y. Sonoda, H. Konomi, M. Kawamoto, T. Takeda, and M. Tanaka (2003). **Total duodenectomy: effects of choecystokinin on the sphincter of oddi motility in conscious dogs.** *Digestive Disease Week Abstracts and Itinerary Planner*: Abstract No. S1160.

Abstract: Objective: Cholecystokinin(CCK) is an important gastrointestinal hormone controlling of the Sphincter of Oddi (SO) motility. The mechanism of CCK action on SO motility is not completely understood. Anatomical and electrophysiological studies suggested direct duodenal neural projections to the SO. However the CCK action via duodeno-SO neural projections under physiological intact animal model has not been reported. The aim of this study is to determine the SO motility response to the CCK via the duodeno-SO neural projections using duodenectomized dogs. Methods: In control group (N=6), Thomas cannula was implanted into the duodenum. In duodenectomy group (N=6), the papilla was sutured to the jejunum and a Thomas cannula implanted opposite to the implanted papilla. In both groups, changes in the SO motility was recorded after intravenous injection of cholecystokinin-octapeptide (20 or 100ng/kg). Results: Injection of 20ng/kg CCK produced initial relaxation followed by contraction in control and no changes in duodenectomy. Injecting of 100ng/kg CCK produced a marked but brief contraction followed by relaxation in controls and only contraction after duodenectomy. Conclusions: (1) Response of SO induced by 20ng/kg CCK was mediated via CCK receptor on the duodenum. (2) The duodenal CCK receptor may be more sensitive to CCK than SO receptor..

Descriptors: digestive system, ingestion and assimilation, methods and techniques, pharmacology, total duodenectomy, clinical techniques, therapeutic and prophylactic techniques, sphincter motility, modulation.

El Bakry, A.A. (2002). **Bowel anastomosis: a comparative study of various surgical techniques.** *Saudi Medical Journal* 23(10): 1232-1236. ISSN: 0379-5284.

Abstract: Objectives: Mechanical suture (stapler) has been in use for bowel anastomosis since the second half of the 20th century, however, it became popular since it was used widely by the United States of America in the late 1960. Since it is more expensive than the conventional method, a local experimental assessment was introduced to compare stapler with conventional methods. Methods: Eighteen local dogs were used, 36 anastomosis were assessed in the animal house operating theater of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia between October 1998 and March 2000. Results: The weight needed to disrupt the anastomosis was more in the stapler technique, the amount of intraperitoneal fluid, adhesion and the inflammatory response in histopathological study were less in the stapler technique. Our study has shown that the stapler technique is superior when compared with conventional bowel anastomosis. Conclusion: We recommend stapler use in bowel anastomosis whenever clinically feasible.

Descriptors: digestive system, ingestion and assimilation, methods and techniques, bowel anastomosis, experimental surgical techniques, laboratory techniques, stapler technique, clinical feasibility, inflammatory response.

Ellis, H. (2008). **The first successful gastrectomy.** *Journal of Perioperative Practice* 18(1): 34. ISSN: 1750-4589.

Abstract: Today, gastrectomy is a routine surgical procedure which any competent abdominal surgeon is expected to be able to perform efficiently and, in a reasonably fit patient, to achieve a speedy and safe recovery. It is worth remembering that the first successful gastrectomy, performed in the late 19th century, was hailed as something of a miracle and opened the way for modern elective abdominal surgery.

Descriptors: faculty, medical history, gastrectomy history, gastroenterostomy history, austria, dogs, eponyms, history, 19th century, models, animal.

Enns, G.M. and M.T. Millan (2008). **Cell-based therapies for metabolic liver disease.** *Molecular Genetics and Metabolism* 95(1-2): 3-10.

NAL Call Number: QP501.B474

Abstract: Liver transplantation is an important therapeutic option for many individuals with metabolic liver disease. Nevertheless, the invasive nature of surgery and limitations of donor organ availability have led to the search for alternatives to whole-organ transplantation. Cell-based therapies have been a particularly active area of investigation in recent years. Hepatocyte transplantations have been performed for a variety of indications, including acute liver failure, end-stage liver disease, and inborn errors of metabolism. Individuals with inborn errors of metabolism who have undergone hepatocyte transplantation have shown clinical improvement and partial correction of the underlying metabolic defect. In most cases, sustained benefits have not been observed. This may be related to inadequate cell dose, variations in the quality of hepatocyte preparations, rejection of the transplanted cells, or senescence of transplanted hepatocytes. Though initial proof of concept with hepatocyte transplantation has been demonstrated by a number of investigators, wide application of this technology has been hindered by the inability to secure a reliable and well-characterized cell

source(s) for transplantation and by the challenges of sustained engraftment and expansion of transplanted cells in vivo. Cell-based therapies, including those based on stem cells or more differentiated progenitor cells, may represent the future of cell transplantation for treatment of metabolic liver disease.

Descriptors: hepatocytes transplantation, liver diseases therapy, metabolic diseases therapy, tissue therapy methods, dogs, mice, models, animal, rats, stem cell transplantation.

Ensminger, W., J. Knol, S. Deremer, E. Wilkinson, S. Walker, D. Williams, and J. Maybaum (2004). **Effects of dexamethasone or celecoxib on biliary toxicity after hepatic arterial infusion of 5-fluorodeoxyuridine in a canine model.** *Cancer Research* 64(1): 311-315. ISSN: 0008-5472.

NAL Call Number: 448.8 C16

Abstract: Previous work has shown that in humans the dose-limiting toxicity for fluorodeoxyuridine (2-fluoro-5'-deoxyuridine (FdUrd)) when administered by hepatic arterial infusion is biliary sclerosis. The current study was undertaken to attempt to modify this toxicity in a canine model that has been demonstrated to closely mimic the clinical situation. Unlike previous studies using this model, in which animals were sacrificed after extensive fibrosis had already occurred, the current experiments were designed so that observations of pathology were made at an earlier time, when the initial inflammatory injury underlying the fibrotic process was still taking place. Implantable pumps were used to deliver FdUrd into the hepatic artery of animals at a rate of 0.3 mg/kg/day in the presence or absence of 10 mg/week dexamethasone or 100 mg/day of celecoxib for 35 days, at which time the animals were beginning to show signs of toxicity. After evaluation for radiological evidence of biliary obstruction, the animals were sacrificed and portions of their livers were processed for examination of microscopic pathology and 2-bromo-5'deoxyuridine labeling index. Dexamethasone treatment protected the animals from biliary sclerosis determined radiologically, further validating this model as being representative of the response in humans. Similarly the Cox-2 inhibitor, celecoxib, appeared to provide protection against radiological changes of biliary stricture, although possibly to a lesser degree than the resultant from dexamethasone. In addition, FdUrd treatment caused elevation of the DNA 2-bromo-5'deoxyuridine labeling index above control levels in biliary epithelial cells. Dexamethasone and celecoxib each significantly attenuated the FdUrd-induced elevation of DNA labeling index in biliary epithelium. These findings demonstrate the usefulness of this canine model for studying the mechanisms of drug-induced biliary sclerosis and reinforce the hypothesis that blocking inflammation may retard the progression of injury that eventually leads to fibrosis. This study suggests that clinical testing of celecoxib as a preventive for hepatic arterial-FdUrd induced biliary damage could prove valuable.

Descriptors: digestive system, ingestion and assimilation, pharmacology, veterinary medicine, medical sciences, biliary obstruction, digestive system disease, biliary sclerosis, drug induced, colorectal cancer, neoplastic disease, infusaid model 400 implantable pump, drug delivery device.

Fujino, Y., K. Kakinoki, Y. Suzuki, S. Li, T. Tanaka, Y. Tanioka, T. Sakai, Y. Ku, and Y. Kuroda (2003). **Successful 24-hour preservation of ischemically damaged canine small intestine by the cavitary two-layer method.** *Transplantation* 76(5): 777-780. ISSN: 0041-1337.
NAL Call Number: QP89.T73
Abstract: Background: The purpose of this study is to examine the possibility of a long-term preservation of the ischemically damaged intestine by the cavitary two-layer method (TLM) in canine small intestinal transplantation. Methods: The grafts were allotransplanted without preservation immediately (group 1) or after 30 minutes of warm ischemia (group 2). The ischemically damaged grafts were also allotransplanted after cold preservation for 24 hours in University of Wisconsin (UW) solution (group 3) or the cavitary TLM (group 4). Seven-day survivals, tissue adenosine triphosphate (ATP) concentrations, absorption tests, and histopathology were examined. Results: seven-day survivals in groups 1, 2, 3, and 4 were 8 of 8, 6 of 8, 0 of 8, and 6 of 8, respectively. In group 4, significant recovery of ATP tissue level was seen after preservation compared with group 3, and absorption function and regeneration of the graft mucosa recovered at day 14. Conclusions: Ischemically damaged canine small intestine could be preserved for 24 hours by the cavitary TLM.
Descriptors: digestive system, ingestion and assimilation, methods and techniques, cavitary two layer method, laboratory techniques, small intestinal transplantation, clinical techniques, therapeutic and prophylactic techniques.

Govendir, M., P.J. Canfield, and D.B. Church (2003). **Cellular proliferation in the canine pancreas after d,l-ethionine dosage as detected by double immunohistochemical labelling.** *Experimental and Toxicologic Pathology* 55(2-3): 129-135. ISSN: 0940-2993.
Abstract: d,l-Ethionine produces pancreatic exocrine necrosis and islet proliferation in hamsters and dogs. As a first step in examining whether induction of islet proliferation has therapeutic applications in animals with exhausted or destroyed insulin-producing beta-cells, we studied pancreatic cellular proliferation after intravenous administration of d,l-ethionine in normal dogs. Double immunohistochemical labelling of pancreatic tissue was used to identify proliferating cells in three groups of six clinically normal crossbred dogs administered d,l-ethionine (100 mg/kg) intravenously three times a week for two weeks. Six additional dogs served as untreated controls. Group I was euthanased and necropsied on day 15 (72 hours after the final dose of ethionine). Groups II and III were euthanased on days 29 and 43 respectively. Utilising markers for proliferating nuclei, insulin and cytokeratin, proliferating cells were classified as acinar, endocrine (both intra or extra-islet), duct or 'other' (i.e. infiltrative or interstitial) and counted under the light microscope (40X magnification). Compared to controls, an increase in the number of proliferating cells was found in all categories except ducts. Acinar cells demonstrated statistically significant ($p < 0.05$) proliferation, greatest two weeks after ethionine cessation continuing over four weeks. The interstitial, infiltrative or 'other' group also showed proliferation, however this was a more immediate response, which substantially decreased two weeks after ethionine administration. Endocrine cells showed only minor and non-significant proliferative activity and were probably not responsible for a significant increase in apparent beta-cell mass. The number of proliferating duct cells was inconsequential and there appeared to be no specific relationship between any cell populations and duct cells.

Descriptors: biochemistry and molecular biophysics, digestive system, ingestion and assimilation, methods and techniques, pancreatic disease, digestive system disease, double immunohistochemical labelling, laboratory techniques, immunohistochemistry, immunologic techniques, cellular proliferation, pancreatic exocrine necrosis.

Graham, M.J., A.R. Bell, H.K. Crewe, C.L. Moorcraft, L. Walker, E.F. Whittaker, and M.S. Lennard (2003). **Mrna and protein expression of dog liver cytochromes p450 in relation to the metabolism of human cyp2c substrates.** *Xenobiotica* 33(3): 225-237. ISSN: 0049-8254.
NAL Call Number: QD415.A1X4
Abstract: 1. Interpretation of novel drug exposure and toxicology data from the dog is tempered by our limited molecular and functional knowledge of dog cytochromes P450 (CYPs). The aim was to study the mRNA and protein expression of hepatic dog CYPs in relation to the metabolism of substrates of human CYP, particularly those of the CYP2C subfamily. 2. The rate of 7-hydroxylation of S-warfarin (CYP2C9 in humans) by dog liver microsomes (mean+-SD from 12 (six male and six female) dogs=10.8+-1.9 fmol mg-1 protein min-1) was 1.5-2 orders of magnitude lower than that in humans. 3. The rate of 4'-hydroxylation of S-mephenytoin, catalysed in humans by CYP2C19, was also low in dog liver (4.6+-1.5 pmol mg-1 protein min-1) compared with human liver. In contrast, the rate of 4'-hydroxylation of the R-enantiomer of mephenytoin by dog liver was much higher. The kinetics of this reaction (range of Km or K0.5 15-22 muM, Vmax 35-59 pmol mg-1 protein min-1, n=4 livers) were consistent with the involvement of a single enzyme. 4. In contrast to our findings for S-mephenytoin, dog liver microsomes 5'-hydroxylated omeprazole (also catalysed by CYP2C19 in humans) at considerably higher rates (range of Km 42-64 muM, Vmax 22-46 pmol mg-1 protein min-1, n=4 livers). 5. For all the substrates except omeprazole, a sex difference in their metabolism was observed in the dog (dextromethorphan N-demethylation: female range=0.7-0.9, male=0.4-0.8 nmol mg-1 protein min-1 ($p<0.02$); S-warfarin 7-hydroxylation: female=9-15.5, male=8-12 fmol mg-1 protein min-1 ($p<0.02$); R-mephenytoin 4'-hydroxylation: female=16-35, male=11.5-19 pmol mg-1 protein min-1 ($p<0.01$); omeprazole 5'-hydroxylation: female=15-20, male 13-22 pmol mg-1 protein min-1 ($p>0.2$)). 6. All dog livers expressed mRNA and CYP3A12, CYP2B11, CYP2C21 proteins, with no sex differences being found. Expression of CYP2C41 mRNA was undetectable in the livers of six of 11 dogs. 7. Correlation analysis suggested that CYP2B11 catalyses the N-demethylation of dextromethorphan (mediated in humans by CYP3A) and the 4'-hydroxylation of mephenytoin (mediated in humans by CYP2C19) in the dog, and that this enzyme and CYP3A12 contribute to S-warfarin 7-hydroxylation (mediated in humans by CYP2C9). 8. In conclusion, we have identified a distinct pattern of hepatic expression of the CYP2C41 gene in the Alderley Park beagle dog. Furthermore, marked differences in the metabolism of human CYP2C substrates were observed in this dog strain compared with humans with respect to rate of reaction, stereoselectivity and CYP enzyme selectivity.
Descriptors: enzymology, biochemistry and molecular biophysics, metabolism.

Horiguchi, K., K.D. Keef, and S.M. Ward (2003). **Distribution of interstitial cells of cajal in tunica muscularis of the canine rectoanal region.** *American Journal of Physiology* 284(5 Part 1): G756-G767. ISSN: 0002-9513.
NAL Call Number: 447.8 Am3

Abstract: Electrical and mechanical activity of the circular muscle layer in the rectoanal region of the gastrointestinal tract undergoes considerable changes in the site of dominant pacemaking activity, frequency, and waveform shape. The present study was performed to determine whether changes in the structural organization of the circular layer or in the density, distribution, and ultrastructure of interstitial cells of Cajal (ICC) could account for this heterogeneity in electrical and mechanical activities. Light microscopy revealed that the structural organization of the circular muscle layer underwent dramatic morphological changes, from a tightly packed layer with poorly defined septa in the proximal rectum to one of discrete muscle bundles separated by large septae in the internal anal sphincter. Kit immunohistochemistry revealed a dense network of ICC along the submucosal and myenteric borders in the rectum, whereas in the internal anal sphincter, ICC were located along the periphery of muscle bundles within the circular layer. Changes in electrical activity within the circular muscle layer can be partially explained by changes in the structure of the muscle layer and changes in the distribution of ICC in the rectoanal region of the gastrointestinal tract.
Descriptors: digestive system, ingestion and assimilation, muscular system, movement and support.

Horikawa, T., F. Hirayama, and K. Uekama (1995). **In-vivo and in-vitro correlation for delayed-release behaviour of a molsidomine/o-carboxymethyl-o-ethyl-beta-cyclodextrin complex in gastric acidity-controlled dogs**. *Journal of Pharmacy and Pharmacology* 47(2): 124-127. ISSN: 0022-3573.
NAL Call Number: RS11.J6
Abstract: The in-vivo absorption behaviour of molsidomine from the delayed-release tablets of an O-carboxymethyl-O-ethyl-beta-cyclodextrin complex was investigated using gastric acidity-controlled dogs under fasted and non-fasted conditions. The in-vitro release profiles were generated by changing the pH of the dissolution medium at different rotation paddle speeds. The absorptivity of molsidomine in the high acidity dog was correlated with the pH-changed release profile (pH 1.2 to 7.0 after 2 h), whereas that in the low acidity dog was correlated with the release profile at a constant pH of 7.0. The absorption in fasted dogs was well correlated with the in vitro release at the low-rotation paddle speed (lt 5 rev min-1), whereas that in the non-fasted dogs was correlated with that of high rotation (100 rev min-1). The present results suggested that the in-vivo delayed-release behaviour of the complex is predictable from the in-vitro release profiles generated using pH-variable dissolution testing apparatus at different rotation speeds of the paddle.
Descriptors: digestive system, ingestion and assimilation, pharmacology, drug release, ph, vasodilator.

Ishibashi, T., H. Hatano, M. Kobayashi, M. Mizobe, and H. Yoshino (1999). **In vivo drug release behavior in dogs from a new colon-targeted delivery system**. *Journal of Controlled Release* 57(1): 45-53. ISSN: 0168-3659.
NAL Call Number: RS201.C64J68
Abstract: The colon-targeted delivery capsule (CTDC), a new capsule-type dosage form for colonic delivery of drugs, was investigated for the in vivo drug release behavior in dogs. A CTDC formulation with prednisolone as a model drug and theophylline as a marker sub-

stance for gastric emptying was prepared for this study. The enteric-coated capsule (ECC) formulation with a similar composition was also prepared as the reference. Both formulations were administered to four beagle dogs, and the drug release behavior thereof was compared. Under fasted condition, ECC released prednisolone and theophylline at the same time within 1 h after the gastric emptying. On the other hand the CTDC released prednisolone at 3.2 h after the gastric emptying. Such release behavior of CTDC was approximately consistent with the results obtained from the in vitro dissolution study, suggesting that the pH-sensing and timed-release functions imparted to the CTDC can work in the gastrointestinal tract of dogs as programmed. Under non-fasted condition, however, the gastric emptying of CTDC was found to be considerably delayed, up to about 14 h, and in this case the in vivo dissolution lag time of prednisolone at the small intestine was shortened to about 1.5 h.
Descriptors: gastroenterology, human medicine, medical sciences, pharmaceuticals, pharmacology, bowel disease, digestive system disease, colon targeted delivery capsule, capsule type dosage form, drug delivery method, pharmacodynamics, drug release, gastric emptying.

Jin, L., I.W. Chen, M. Chiba, and J.H. Lin (2003). **Interaction with indinavir to enhance systemic exposure of an investigational hiv protease inhibitor in rats, dogs and monkeys.** *Xenobiotica* 33(6): 643-654. ISSN: 0049-8254.
NAL Call Number: QD415.A1X4
Abstract: 1. The use of a beneficial interaction between indinavir and compound A, a potent investigational HIV protease inhibitor to enhance systemic exposure of compound A, was investigated. 2. When administrated alone, compound A underwent extensive hepatic first-pass metabolism in rats and monkeys, resulting in low oral bioavailability. 3. In vitro studies with liver microsomes revealed that compound A metabolism was mediated exclusively by CYP3A enzymes in rats, dogs and monkeys. Indinavir, which also was metabolized predominantly by CYP3A enzymes, extensively inhibited compound A metabolism in microsomes, whereas compound A showed weak inhibitory potency on indinavir metabolism. 4. Consistent with in vitro observations, co-administration of the two compounds resulted in a 17-fold increase in oral AUC of compound A in rats owing to the inhibition of metabolism of compound A by indinavir, whereas compound A did not affect indinavir metabolism as indicated by the unchanged indinavir AUC. Similarly, the systemic exposure of compound A in dogs and monkeys was increased substantially following oral co-administration with indinavir by 7- and > 50-fold, respectively. 5. Enhancement in compound A systemic exposure by indinavir in humans, as predicted based on the in vivo animal and in vitro human liver microsomal data, was confirmed in subsequent clinical studies.
Descriptors: digestive system, ingestion and assimilation, metabolism, pharmacology, extensive hepatic first pass metabolism.

Kawarada, Y. (2001). **[Hepatopancreatoduodenectomy (HPD).]**. *Nippon Geka Gakkai Zasshi.* 102(2): 195-8. ISSN: 0301-4894.
Abstract: Since the mid-1980s, simultaneous major resection of the liver and the pancreatic head, so-called HPD, has been performed in Japan to improve the survival rate of patients with advanced biliary tract carcinoma. We conducted a study of HPD in dogs in our laboratory from 1986 to 1989 and found that 75% died following 70% hepatectomy with more than 92% pancreatectomy and that only 25% survived. The main cause of death was liver

failure. A clinical review of the operative procedures and the outcome of HPD was performed by Mizumoto et al. in our department in 1989. They collected data on 241 patients who underwent HPD for advanced biliary tract carcinoma throughout Japan. The postoperative morbidity and mortality rates after HPD were higher than after other major surgeries. The prognosis after HPD has improved in recent years because of preservation of adequate hepatic or pancreatic parenchyma, improvements in surgical technique, and strict perioperative care. Therefore we plan to review the operative procedures and outcome of HPD again in 2000.

Descriptors: animal model, dogs, major resection, liver, pancrease, Japan, liver failure, mobidity, mortality, human data.

Language of Text: Japanese.

Knapp, B.K., C.M. Parsons, K.S. Swanson, and G.C.J. Fahey (2008). **Physiological responses to novel carbohydrates as assessed using canine and avian models.** *Journal of Agricultural and Food Chemistry* 56(17): 7999-8006.

NAL Call Number: 381 J8223

Abstract: The objective was to quantify in vitro digestion, true metabolizable energy (TME(n)) content, glycemic and insulinemic responses, and gastrointestinal tolerance to fructose (Fruc), maltodextrin (Malt), polydextrose (Poly), pullulan (Pull), resistant starch (RS), sorbitol (Sorb), and xanthan gum (Xan). Limited digestion of RS, Poly, and Xan occurred. Fruc, Malt, and Sorb resulted in the highest ($P < 0.05$) TME(n) values, Pull was intermediate, and RS and Poly were lowest. Malt had the highest ($P < 0.05$) area under the curve for glucose and insulin in the glycemic tests. Gastrointestinal tolerance was examined for diets containing carbohydrates at either 100 or 200% of the adequate intake (AI) value for dietary fiber. At 100% and 200% AI, Malt, RS, and Sorb resulted in ideal fecal scores, while Pull and Xan resulted in looser stools and Poly resulted in diarrhea. The carbohydrates studied varied widely in physiological outcomes. Certain carbohydrates could potentially benefit large bowel health.

Descriptors: blood glucose analysis, carbohydrates pharmacology, digestion drug effects, energy metabolism drug effects, gastrointestinal tract drug effects, insulin blood, chickens, dogs, fructose pharmacology, models, animal, polysaccharides pharmacology.

Marcovich, R., A.L. Williams, B.D. Seifman, and J.S.J. Wolf (2001). **A canine model to assess the biochemical stress response to laparoscopic and open surgery**. *Journal of Endourology* 15(10): 1005-1008. ISSN: 0892-7790.

Abstract: Purpose: To develop an animal model to assess the stress response to open and laparoscopic surgery. Such a model would allow objective physiologic assessment of the putative benefits of laparoscopy and provide a framework in which to compare modifications in operative and anesthetic technique that might decrease the stress of surgery. Materials and Methods: Mongrel dogs underwent laparoscopic (N = 12) or open surgical (N = 12) left nephrectomy. In 11 control animals, after induction of anesthesia and line placement, the animal underwent either no intervention (open surgery sham; N = 6) or pneumoperitoneum only (laparoscopic sham; N = 5). Serum glucose and cortisol were measured preoperatively, at skin closure, and at 4, 8, and 24 hours postoperatively. Values at each time point were compared in the laparoscopic and open surgical nephrectomy groups and in each of the two

nephrectomy groups and their respective shams. Results: Compared with baseline, there was a sharp rise in serum cortisol at the time of skin closure, with a gradual decline to baseline values by 24 hours, in all experimental animals. Significantly lower serum cortisol concentrations were seen at 4 and 8 hours postoperatively in the laparoscopic group than in the open surgery group. Cortisol was significantly higher in the open group than in the sham-open group at all time points, whereas cortisol was greater in the laparoscopic group than in the pneumoperitoneum-only group only at the 4-hour time point. No differences were seen in serum glucose between groups. Conclusions: The serum cortisol concentration appears to be a good measure of surgical stress in the canine model. The rapid decline in serum cortisol after laparoscopy compared with open surgery may indicate a lesser degree, or quicker resolution, of surgical stress in the former. Furthermore, the similarity in cortisol curves between laparoscopy and pneumoperitoneum only suggests that surgical stress in laparoscopic surgery may be attributable mainly to the effects of pneumoperitoneum.
Descriptors: endocrine system, chemical coordination and homeostasis, methods and techniques, pneumoperitoneum, digestive system disease, laparoscopic nephrectomy, open surgical nephrectomy, surgical method, biochemical stress response, surgical stress.

Mata Bilbao, M.L., C. Andres Lacueva, E. Roura, O. Jauregui, E. Escribano, C. Torre, and R.M. Lamuela Raventos (2008). **Absorption and pharmacokinetics of green tea catechins in beagles.** *British Journal of Nutrition* 100(3): 496-502. ISSN: 0007-1145.
NAL Call Number: 389.8 B773
Abstract: The present study evaluates for the first time in dogs, the kinetics of green tea catechins and their metabolic forms in plasma and urine. Ten beagles were administered 173 mg (12.35 mg/kg body weight) of catechins as a green tea extract, in capsules. Blood samples were collected during 24 h after intake and urine samples were collected during the following periods of time: 0-2, 2-6, 6-8 and 8-24 h. Two catechins with a galloyl moiety and three conjugated metabolites were detected in plasma. Most of the detected forms in plasma reached their maximum plasma concentration (Cmax) at around 1 h. Median Cmax for (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin glucuronide (EGC-glucuronide), (-)-epicatechin glucuronide (EC-glucuronide), (-)-epicatechin sulphate (EC-sulphate) were 0.3 (range 0.1-1.9), 0.1 (range 0-0.4), 0.8 (range 0.2-3.9), 0.2 (range 0.1-1.7) and 1 (range 0.3-3.4) micromol/l, respectively. The areas under the plasma concentration v. time curves (AUC0 --> 24) were 427 (range 102-1185) micromol/l x min for EGC-glucuronide, 112 (range 53-919) micromol/l x min for EC-sulphate, 71 (range 26-306) micromol/l x min for EGCG, 40 (range 12-258) micromol/l x min for EC-glucuronide and 14 (range 0.1-124) micromol/l x min for ECG. The values of mean residence time (MRT0 --> 24) were 5 (range 2-16), 2 (range 1-11), 10 (range 2-13), 3 (range 2-16) and 2.4 (range 1-18) h for EGCG, ECG, EGC-glucuronide, EC-glucuronide and EC-sulphate, respectively. In urine, catechins were present as conjugated forms, suggesting bile excretion of EGCG and ECG. Green tea catechins are absorbed following an oral administration and EGC-glucuronide is the metabolic form that remains in the organism for a longer period of time, suggesting that this compound could suffer an enterohepatic cycle.
Descriptors: antioxidants pharmacokinetics, catechin pharmacokinetics, dogs metabolism, tea, administration, oral, biological availability, biotransformation, catechin analogs and derivatives, catechin analysis, catechin chemistry, catechin metabolism, glucuronides analysis,

glucuronides metabolism, intestinal absorption drug effects, models, animal, sulfuric acid esters analysis, sulfuric acid esters metabolism, time factors.

Mata Bilbao, M.L., C. Andres Lacueva, E. Roura, O. Jauregui, E. Escribano, C. Torre, and R.M. Lamuela Raventos (2007). **Absorption and pharmacokinetics of grapefruit flavanones in beagles.** *British Journal of Nutrition* 98(1): 86-92. ISSN: 0007-1145.
NAL Call Number: 389.8 B773
Abstract: The present study evaluated the pharmacokinetics of three different grapefruit flavanone forms in dog plasma and demonstrated their absorption after an oral intake of a grapefruit extract; pharmacokinetic parameters of these forms were also determined. Ten healthy beagles were administered 70 mg citrus flavonoids as a grapefruit extract contained in capsules, while two additional dogs were used as controls and given an excipient. The grapefruit flavanone naringin, along with its metabolites naringenin and naringenin glucuronide, was detected in dog plasma. Blood samples were collected between 0 and 24 h after administration of the extract. Naringin reached its maximun plasma concentration at around 80 min, whereas naringenin and naringenin glucuronide reached their maximun plasma concentrations at around 20 and 30 min, respectively. Maximum plasma concentrations of naringin, naringenin and naringenin glucuronide (medians and ranges) were 0.24 (0.05-2.08), 0.021 (0.001-0.3) and 0.09 (0.034-0.12) micromol/l, respectively. The areas under the curves were 23.16 l (14.04-70.62) min x micromol/for nariningin, 1.78 (0.09-4.95) min x micromol/l for naringenin and 22.5 (2.74-99.23) min x micromol/l for naringenin glucuronide. The median and range values for mean residence time were 3.3 (1.5-9.3), 2.8 (0.8-11.2) and 8.0 (2.3-13.1) h for naringin, naringenin and naringenin glucuronide, respectively. The results of the present study demonstrate the absorption of grapefruit flavanones via the presence of their metabolites in plasma, thus making an important contribution to the field since the biological activities ascribed to these compounds rely on their specific forms of absorption.
Descriptors: citrus paradisi chemistry, flavanones pharmacokinetics, absorption, administration, oral, biological availability, dogs, flavanones administration and dosage, flavanones blood, intestinal absorption, models, animal, plant extracts administration and dosage, plant extracts pharmacokinetics.

Mcginnity, D.F., M.G. Soars, R.A. Urbanowicz, and R.J. Riley (2004). **Evaluation of fresh and cryopreserved hepatocytes as in vitro drug metabolism tools for the prediction of metabolic clearance**. *Drug Metabolism and Disposition* 32(11): 1247-1253. ISSN: 0090-9556.
NAL Call Number: RM301.35.D78
Abstract: The intrinsic clearances (CLint) of 50 neutral and basic marketed drugs were determined in fresh human hepatocytes and the data used to predict human in vivo hepatic metabolic clearance (CLmet). A statistically significant correlation between scaled CLmet and actual CLmet was observed (r2 = 0.48, p 0.05), and for 73% of the drugs studied, scaled clearances were within 2-fold of the actual clearance. These data have shown that CLint data generated in human hepatocytes can be used to provide estimates of human hepatic CLmet for both phase I and phase II processes. In addition, the utility of commercial and in-house cryopreserved hepatocytes was assessed by comparing with data derived from fresh cells.
A set of 14 drugs metabolized by the major human cytochromes P450 (P450s) CYP1A2, 2C9, 2C19, 2D6, and 3A4) and uridine diphosphate glucuronosyltransferases (UGT1A1,

1A4, 1A9, and 2B7) have been used to characterize the activity of freshly isolated and cryopreserved human and dog hepatocytes. The cryopreserved human and dog cells retained on average 94% and 81%, respectively, of the CLint determined in fresh cells. Cryopreserved hepatocytes retain their full activity for more than 1 year in liquid N2 and are thus a flexible resource of hepatocytes for in vitro assays. In summary, this laboratory has successfully cryopreserved human and dog hepatocytes as assessed by the turnover of prototypic P450 and UGT substrates, and both fresh and cryopreserved human hepatocytes may be used for the prediction of human hepatic CLmet.
Descriptors: digestive system, ingestion and assimilation, enzymology, biochemistry and molecular biophysics, metabolism, hplc, high performance liquid chromatography, chromatographic techniques, laboratory techniques, intrinsic clearance, metabolic clearance.

Mellinger, J.D., B.V. MacFadyen, R.A. Kozarek, N.D. Soper, D.H. Birkett, and L.L. Swanstrom (2007). **Initial experience with a novel endoscopic device allowing intragastric manipulation and plication.** *Surgical Endoscopy* 21(6): 1002-5.
NAL Call Number: RD33.53
Abstract: BACKGROUND: Current developments in intraluminal and transluminal natural orifice surgery are limited by issues of access, tissue manipulation, and secure tissue approximation/closure. This report describes an initial laboratory experience with a novel tissue approximation and suturing device. The device is deployed via a previously described platform and is 6 mm in diameter. Desirable qualities of this tissue approximation/closure device include robust tissue grasping, minimal tissue trauma, fully visualized anchor placement via off-axis needle and anchor deployment, full reloadability without instrument withdrawal, single-operator operating capability, torque-stable manipulability, and operator-controlled tension setting of tissue anchor pairs. METHOD: The device was trialed in performing several maneuvers in porcine or canine models. The features of the system allowed bimanual tissue manipulation, full-thickness tissue approximation and plication, and secure closure of an ex vivo gastrotomy hole similar to that used during transluminal surgical interventions. CONCLUSIONS: This device appears to offer promise in achieving more complex endoluminal and potentially transluminal tasks, including secure suture closure of tissue defects and access holes. As such, devices of this type may prove useful in addressing some of the identified barriers to further development of natural orifice surgical intervention. Further investigation of the qualities and capabilities of this device in these settings is warranted.
Descriptors: gastroscopy, stomach surgery, suture techniques instrumentation, dogs, gastroscopes, models, animal, swine.

Mueller, T., B. Van-De-Sluis, A. Zhernakova, E. Van-Binsbergen, A.-R. Janecke, A. Bavdekar, A. Pandit, H. Weirich-Schwaiger, H. Witt, H. Ellemunter, J. Deutsch, H. Denk, W. Mueller, I. Sternlieb, M.-S. Tanner, and C. Wijmenga (2003). **The canine copper toxicosis gene murr1 does not cause non-wilsonian hepatic copper toxicosis.** *Journal of Hepatology* 38(2): 164-168. ISSN: 0168-8278.
NAL Call Number: RC845
Abstract: Background: Non-Wilsonian hepatic copper toxicosis includes Indian childhood cirrhosis (ICC), endemic Tyrolean infantile cirrhosis (ETIC) and the non-Indian disease known as idiopathic copper toxicosis (ICT). These entities resemble the hepatic copper over-

load observed in livers of Bedlington terriers with respect to their clinical presentation and biochemical and histological findings. We recently cloned the gene causing copper toxicosis in Bedlington terriers, MURR1, as well as the orthologous human gene on chromosome 2p13-p16. Aim: To study the human orthologue of the canine copper toxicosis gene as a candidate gene for ICC, ETIC, and ICT. Methods: We sequenced the exons and the intron-exon boundaries of the human MURR1 gene in 12 patients with classical ICC, one patient with ETIC, and 10 patients with ICT to see whether these patients display any mutations in the human orthologue of the canine copper toxicosis gene. Results: No mutations in the MURR1 gene, including the intron-exon boundaries, were identified in a total of 23 patients with non-Wilsonian hepatic copper toxicosis. Conclusions: Our results demonstrate that copper toxicosis in Bedlington terriers is not an animal model for the non-Wilsonian hepatic copper toxicosis described in this study.

Descriptors: gastroenterology, human medicine, medical sciences, molecular genetics, biochemistry and molecular biophysics, toxicology, Indian childhood cirrhosis, digestive system disease, etiology, endemic Tyrolean infantile cirrhosis, idiopathic copper toxicosis, metabolic disease, toxicity, etiology, non Wilsonian hepatic copper toxicosis, metabolic disease, toxicity, pathology, clinical presentation.

Mutafova Yambolieva, V.N., K. O'driscoll, A. Farrelly, S.M. Ward, and K.D. Keef (2003). **Spatial localization and properties of pacemaker potentials in the canine rectoanal region.** *American Journal of Physiology* 284(5 Part 1): G748-G755. ISSN: 0002-9513.

NAL Call Number: 447.8 Am3

Abstract: The present study investigated the spatial organization of electrical activity in the canine rectoanal region and its relationship to motility patterns. Contraction and resting membrane potential (Em) were measured from strips of circular muscle isolated 0.5-8 cm from the anal verge. Rapid frequency (25 cycles/min (cpm)) Em oscillations (MPOs, 12 mV amplitude) were present across the thickness of the internal anal sphincter (IAS; 0.5 cm) and Em was constant (-52 mV). Between the IAS and the proximal rectum an 18 mV gradient in Em developed across the muscle thickness with the submucosal edge at -70 mV and MPOs were replaced with slow waves (20 mV amplitude, 6 cpm). Slow waves were of greatest amplitude at the submucosal edge. Nifedipine (1 muM) abolished MPOs but not slow waves. Contractile frequency changes were commensurate with the changes in pacemaker frequency. Our results suggest that changing motility patterns in the rectoanal region are associated with differences in the characteristics of pacemaker potentials as well as differences in the sites from which these potentials emanate.

Descriptors: digestive system, ingestion and assimilation, muscular system, movement and support, pacemaker potentials, spatial localization.

Nagaya, M., S. Kubota, N. Suzuki, M. Tadokoro, and K. Akashi (2004). **Evaluation of thermoreversible gelation polymer for regeneration of focal liver injury.** *European Surgical Research* 36(2): 95-103. ISSN: 0014-312X.

Abstract: Liver injuries are often associated with complications including infection of the dead space, bleeding, leakage of bile and so on. We have recently developed a thermoreversible gelation polymer (TGP) which provides a good healing environment for wounds and possibly reduces complications. The purpose of this study was to evaluate whether adequate

regeneration occurred with a liver defect by using TGP. The sol-gel transition of TGP is reversibly controlled by temperature; TGP is soluble below a lower critical solution temperature (LCST) of 22degreeC, and becomes solid above the LCST. Soluble TGP can reach anywhere, and gelation of TGP occurs at the wound surface by body temperature to fill the wound/cavity. A section of median part of the left lobe comprising 3% (2 X 2 cm wide and 1 cm deep) of the liver was resected, and the Beagle dogs were assigned to three groups: 'resection alone group', 'resection + fibrin glue (FG) group' and 'resection + TGP group'. The resection alone group and the resection + FG group showed severe fibrosis at week 12, and a scarring was clearly visible. The resection + TGP group showed almost complete healing by week 4, with no adhesion and recession of the wound; the resection site was completely filled with TGP, liver-like capsule organoids emerged to cover the wound and neovascularization was observed within the organoids. Furthermore, the resected liver regenerated completely by week 12, TGP was replaced by hepatocytes, and the presence of hepatic lobules confirmed structural reorganization. The number of RCA-1-positive macrophages accumulating around the wound was significantly reduced in the resection + TGP group compared to the other two groups. In the early stage of liver resection and regeneration, TGP seemed to suppress the accumulation of macrophages and stellate cells. In the late stage, when massive inflammatory cell accumulation had subsided, TGP was degraded, that may contribute to avoid unnecessary inhibition of the liver regeneration process. Collectively, TGP may induce efficient regeneration by reducing the fibrosis and enhancing proliferation, even with a minor liver defect. Because TGP has good biocompatibility, it may become useful as an ideal biomaterial for the treatment of liver injuries.
Descriptors: digestive system, ingestion and assimilation, methods and techniques, focal liver injury, digestive system disease, injury, resection, experimental surgical techniques, laboratory techniques, liver regeneration, lower critical solution temperature.

Naitoh, T., A. Garcia Ruiz, A. Darvish, A. Vladisavljevic, S. Matsuno, and M. Gagner (1997).
Gastrointestinal transit and stress response after laparoscopic vs. Conventional distal pancreatectomy in dogs. *Gastroenterology* 112(4 SUPPL.): A1461. ISSN: 0016-5085.
NAL Call Number: RC799.G37
Descriptors: digestive system, ingestion and assimilation, surgery, medical sciences, conventional distal pancreatectomy, digestive system, gastrointestinal transit, laparoscopic distal pancreatectomy, stress response, surgical method.

Nazarenko, N.A., V.A. Vishnevskii, N.D. Skuba, B.V. Vtiurin, I.M. Buriev, and A.V. Chzhao (2001).
Portal'naia embolizatsiia (eksperimental'no-morfologicheskoe issledovanie). *Khirurgiia (Mosk).* 4: 35-38. ISSN: 0023-1207.
Abstract: Results of experimental-morphological study of influence of unilobar portal embolization by biologic occlusive material RABROM on the liver of 6 laboratory animals are presented. It is shown that portal venous embolization leads to focal necrosis of parenchyma of embolized hepatic lobe, it atrophy and formation of portal cirrhosis. In non-embolized hepatic lobe the distinct signs of increased regeneration and hypertrophy of hepatocytes were revealed. RABROM didn't lead to damage and inflammatory changes of vascular wall that testifies to it biologic inertia. It is recommended to use the method of portal venous embolization for preparation of patients with low functional hepatic reserve for extensive

resections.
Descriptors: animal model, unilobar portal embolization, biologic occlusive material, focal necrosis, functional hepatic reserve.

Okabe, S., T. Fujishita, and K. Jinbo (2003). **New target for the inhibitors of gastric acid secretion. Inhibition of myosin and actin activities via the apical membrane of parietal cells in dogs.** *Folia Pharmacologica Japonica* 122(1): 74P-77P. ISSN: 0015-5691.
Abstract: This report aims to highlight drugs that are able to inhibit parietal cells from the luminal side, resulting in suppressed gastric acid secretion. Histamine 2HCl was i.v. given continuously to obtain a submaximal stimulation of gastric acid secretion. Wortmannin and ME 3407 (a myosin light chain kinase inhibitor) and cytocharasin D (actin polymerizing inhibitor) were locally applied to denervated gastric pouches prepared in dogs for 5 to 30 min. Each drug, administered 0.5 hr before or 1 hr after histamine infusion was commenced, significantly inhibited stimulated-gastric acid secretion in a time-dependent manner. The antisecretory effect persisted for more than 24 hrs in the case of Wortmannin and 9 hr in the case of ME 3407 at a dosage 1 and 3 mg/pouch for 30 min, respectively. ME 2407, however, had no antisecretory effect when i.v. administered after histamine infusion, or orally administered before histamine infusion. Such results strongly suggest that the apical membrane of parietal cells possesses a ME 4307, Wortmannin and cytocharasin D sensitive portion similar to the basolateral membrane that usually mediates gastric acid secretion. The apical membrane represents an intriguing target for developing new antisecretory drugs, as well as for elucidating the functional features of parietal cells.
Descriptors: biochemistry and molecular biophysics, digestive system, ingestion and assimilation, veterinary medicine, medical sciences.
Language of Text: Japanese.

Oliveira, A.L., N. Jamel, D.P. Lacombe, M.D. Goncalves, E.J. Abilio, J.E. Manso, and A.C. Costa (2007). **Use of intraluminal protection in colonic anastomosis in dogs.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(1): 57-62. ISSN: 0102-8650.
Abstract: PURPOSE: To test the use of intraluminal protection in colonic anastomosis without intestinal cleansing. The intraluminal liner was fashioned from porcine submucosa preserved in glycerin and then fixed 10 cm anteriorly to the anastomotic site. This technique was compared with the one used in termino-terminal colonic anastomosis without intraluminal protection. METHODS: Twenty-eight dogs were divided into two groups of fourteen animals each. Clinical and histopathological tests were performed on the fourth and twenty-first postoperative days. RESULTS: The morbidity and mortality rates were higher in animals that did not receive the intraluminal liner. Histopathological examinations in animals in which the intraluminal liner was used showed better healing, characterized by milder inflammation and increased amount of collagen. CONCLUSION: It can be concluded that the use of intraluminal protection decreases complication rates in colonic anastomosis and promotes better healing.
Descriptors: colon surgery, glycerol therapeutic use, intestinal mucosa transplantation, anastomosis, surgical adverse effects, anastomosis, surgical methods, anastomosis, surgical

mortality, collagen, dogs, inflammation, models, animal, surgical wound dehiscence etiology, swine, wound healing.

Ouguerram, K., P. Nguyen, M. Krempf, E. Pouteau, F. Briand, E. Bailhache, and T. Magot (2004). **Selective uptake of high density lipoproteins cholesteryl ester in the dog, a species lacking in cholesteryl ester transfer protein activity: an in vivo approach using stable isotopes**. *Comparative Biochemistry and Physiology B, Biochemistry and Molecular Biology* 138(4): 339-345. ISSN: 1096-4959.

NAL Call Number: QP501.C6

Abstract: Amongst the processes involved in the reverse cholesterol transport (RCT) from organs to liver, including high density lipoproteins-apolipoprotein AI (HDL-apoAI) dependent tissue uptake and cholesteryl ester transfer protein (CETP)-mediated transfers, the selective uptake of cholesteryl ester (CE) is of increasing interest through its antiatherogenic role. The purpose of this report is to develop a simple protocol allowing study of this process in an animal model with easier quantification of CE selective uptake. The dog was chosen essentially because this animal has a low CETP activity and an appropriate size to conduce a kinetic study. Tracer kinetics were performed to estimate in vivo the contributions of the pathways involved in HDL-CE turnover in dogs. Stable isotopes, 13C-acetate and D3-leucine as labeled precursors of CE and apoAI, were infused to fasting dogs. Isotopic enrichments were monitored in plasma unesterified cholesterol and in HDL-CE and apoAI by mass spectrometry. Kinetics were analyzed using compartmental modeling. Results concerned the measurement of the activity of cholesterol esterification (0.13+or-0.032 h-1), rate of HDL-apoAI catabolism (0.024+or-0.012 h-1), HDL-CE turnover (0.062+or-0.010 h-1) and CE selective uptake (0.038+or-0.014 h-1). Our results show that CE in dogs is mainly eliminated by selective uptake of HDL-CE (60% of HDL-CE turnover), unlike in other species studied by similar methods in our laboratory. This study shows that among species used to analyze cholesterol metabolism, the dog appears to be the animal in whom HDL-CE selective uptake represents the largest part of HDL-CE turnover.

Descriptors: analytical methods, animal models, cholesterol, cholesteryl ester transfer protein, cholesteryl esters, high density lipoprotein, isotopes, uptake.

Renard, E. (2008). **Implantable continuous glucose sensors.** *Current Diabetes Reviews* 4(3): 169-74.

Abstract: Because of the limits of wearable needle-type or microdialysis-based enzymatic sensors in clinical use, fully implantable glucose monitoring systems (IGMS) represent a promising alternative. Long-term use reducing impact of invasiveness due to implantation, less frequent calibration needs because of a more stable tissue environment around the sensor and potential easier inclusion in a closed-loop insulin delivery system are the expected benefits of IGMS. First experiences with subcutaneous and intravenous IGMS have been recently collected in pilot studies. While no severe adverse events have been reported, biointerface issues have been responsible for the failures of IGMS. Tissue reactions around implanted subcutaneous devices and damages of intravenous sensors due to shearing forces of blood flow impaired IGMS function and longevity. In functioning systems, accuracy of glucose measurement reached satisfactory levels for average durations of about 120 days with subcutaneous IGMS and 259 days with intravenous sensors. Moreover, sensor information could help to improve time spent in normal glucose range when provided to patients wearing subcutaneous

IGMS and allowed safe and effective closed-loop glucose control when intravenous sensors were connected to implanted pumps using intra-peritoneal insulin delivery. These data could open a favourable perspective for IGMS after improvement of biointerface conditions and if compatible with an affordable cost.

Descriptors: blood glucose analysis, diabetes mellitus, type 1 blood, monitoring, physiologic instrumentation, prostheses and implants, biosensing techniques instrumentation, biosensing techniques methods, dogs, equipment design, models, animal, user computer interface.

Salahi, H., S. Nikeghbalian, A.R. Shamsaee, E. Kheradmand, B. Sabet, H. Jalaeian, B. Geramizadeh, N. Tanideh, and S.A. Malek Hosseini (2007). **Comparison of early outcome and histologic findings of enteric drainage with bladder drainage in pancreas transplantation of dogs.** *Transplantation Proceedings* 39(4): 1255-6. ISSN: 0041-1345.

NAL Call Number: RD120.7.T68

Abstract: BACKGROUND: The clinical and pathological findings of enteric-drained (ED) versus bladder-drained (BD) pancreas transplantation are still controversial. In this study, we compared early outcome and histological findings of these 2 methods. METHODS: In an experimental animal model, after diabetization, 16 dogs were randomly divided into 2 groups. In the first group, the pancreas was transplanted with enteric drainage, and in the second group, with bladder drainage. We evaluated early clinical and pathological outcomes. RESULTS: The mean survival time was 11.25 +/- 5.0 (range, 5-20) days for group 1 and 13.6 +/- 7.2 (range, 3-23) days for group 2 (P>.05). Fasting blood sugar values (FBS) before transplantation were 279 +/- 26.8 mg/dL versus 278 +/- 41.6 mg/dL, respectively (P>.05). Two weeks postoperative serum FBS had decreased to 84.9 +/- 2.9 versus 84.2 +/- 0.98, respectively (P>.05). Serum amylase in the BD and ED groups were 378.5 +/- 328 versus 422.6 +/- 54.7 mg/dL, respectively (P>.05). Early leakage was not observed in dogs with BD, whereas it was 37.5% among dogs with ED (P<.05). Clinical and pathological evidences of pancreatic necrosis occurred in 37.5% of dogs with BD versus 62.5% of dogs with ED (P>.05). DISCUSSION: Although the early outcomes of these drainage methods (ED vs BD) were statistically similar more dogs with ED experienced early complications than with BD.

Descriptors: pancreas transplantation methods, pancreas transplantation physiology, dogs, drainage methods, models, animal, pancreas transplantation mortality, pancreas transplantation pathology, survival analysis, treatment outcome, urinary bladder surgery.

Schwach Abdellaoui, K., M. Moreau, M. Schneider, B. Boisramc, and R. Gurny (2002). **Controlled delivery of metoclopramide using an injectable semi-solid poly(ortho ester) for veterinary application.** *International Journal of Pharmaceutics* 248(1-2): 31-7. ISSN: 0378-5173.

NAL Call Number: RS122.A1I5

Abstract: In animal health care, current therapeutic regimens for gastrointestinal disorders require repeated oral or parenteral dosage forms of anti-emetic agents. However, fluctuations of plasma concentrations produce severe side effects. The aim of this work is to develop a subcutaneous and biodegradable controlled release system containing metoclopramide (MTC). Semi-solid poly(ortho ester)s (POE) prepared by a transesterification reaction between trimethyl orthoacetate and 1,2,6,-hexanetriol were investigated as injectable bioerodible polymers for the controlled release of MTC. MTC is present in the polymeric

matrix as a solubilised form and it is released rapidly from the POE by erosion and diffusion because of its acidic character and its high hydrosolubility. If a manual injection is desired, only low molecular weight can be used. However, low molecular weight POEs release the drug rapidly. In order to extend polymer lifetime and decrease drug release rate, a sparingly water-soluble base Mg(OH)(2) was incorporated to the formulation. It was possible to produce low molecular weight POE that can be manually injected and releasing MTC over a period of several days.

Descriptors: health care, gastrointestinal system, anti-emetic agents, metoclopramide (MTC), pharmacology.

Sonoda, Y., M. Dong, H. Konomi, M. Kawamoto, K. Kobayashi, K. Yamaguchi, and M. Tanaka (2003). **Role of duodenum on sphincter of oddi motility in conscious dogs.** *Digestive Diseases and Sciences* 48(9): 1693-1700. ISSN: 0163-2116.

NAL Call Number: 448.8 AM324

Abstract: Our aim was to determine the role of the duodenum in controlling sphincter of Oddi motility using conscious dogs after total duodenectomy. In a control group (N = 6), a cannula was implanted into the duodenum opposite to the papilla to allow retrograde sphincter manometry. In a duodenectomy group (N = 6), the papillae were preserved at total duodenectomy and sutured to the jejunum anastomosed to the stomach (neoduodenum). The cannula was implanted opposite to the implanted papillae. Interdigestive and postprandial sphincter and duodental or neoduodenal motility were recorded by manometric and myoelectric methods. Duodenectomy disrupted sphincter cyclic motility associated with the intestinal migrating motor complex and increased sphincter activity throughout the cycle. Sphincter activity increased immediately after feeding and did not differ between the two groups. In conclusion, during the interdigestive period, the duodenum has a distinct role in regulating sphincter cyclic motility. The initiation of the fed pattern of sphincter motility does not need the duodenum.

Descriptors: digestive system, ingestion and assimilation, surgery, medical sciences, myoelectric method, laboratory techniques, retrograde sphincter manometry, clinical techniques, total duodenectomy, experimental surgical techniques, laboratory techniques, cyclic motility, duodenal, neoduodenal motility, fed pattern initiation, feeding, interdigestive period, interdigestive sphincter motility, intestinal migrating motor complex, postprandial sphincter motility, sphincter cyclic motility.

Stagner, J.I., H.L. Rilo, and K.K. White (2007). **The pancreas as an islet transplantation site. Confirmation in a syngeneic rodent and canine autotransplant model.** *JOP Journal of the Pancreas* 8(5): 628-36.

Abstract: CONTEXT: The availability of islet transplantation is limited by both the number of donor pancreata and the number of islets required for successful transplantation. There is evidence that the liver presents a less than optimal environment for islets that contributes to short- and long-term beta cell destruction or failure. OBJECTIVE: It is our hypothesis that the pancreas is a suitable transplant site and may require fewer islets than standard sites such as the liver or kidney, and could lead to improvements in transplantation outcomes. METHODS: To test this hypothesis both a rodent and a canine model were used. Syngeneic rat islets were transplanted to the pancreas, liver, or kidney of Lewis rats. Fasting blood

glucose levels were compared for three months as an index of islet function. Dogs received an islet autotransplant to a pancreatic remnant. Insulin and glucose concentrations were followed for six months. RESULTS: In the rat, normoglycemia was maintained with 600 islets transplanted in the pancreas in contrast to the liver (3,200 islets) or kidney (1,000-2,000 islets). Dogs remained normoglycemic after receiving an intra-pancreatic islet transplant (mean 7,640+/-3,600 islets). There was no evidence of pancreatitis or nutritional deficiency in either species. CONCLUSIONS: The pancreas should be considered as an islet transplant site. The pancreas is the native milieu for islets, and offers the advantage of requiring fewer islets than other conventional sites, thereby increasing the possibility that one donor pancreas may serve one or more recipients.
Descriptors: diabetes mellitus, experimental surgery, islets of langerhans transplantation methods, pancreas surgery, dogs, models, animal, rats, rats, inbred lew, transplantation, autologous.

Sun, S., S. Wang, N. Ge, T. Lei, Q. Lu, Z. Zhou, A. Yang, Z. Wang, and M. Sun (2007). **Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model.** *Endoscopy* 39(6): 530-4.
Abstract: BACKGROUND AND STUDY AIM: Interstitial chemotherapy using surgically implanted, biodegradable polymers has been reported. Our aim in this study was to investigate the feasibility and safety of endoscopic ultrasound- (EUS-) guided interstitial chemotherapy of the pancreas in a canine model. MATERIALS AND METHODS: A therapeutic 19-gauge needle with a large channel was inserted into the pancreas under EUS guidance. The polymers for sustained intratumoral release of 5-fluorouracil were implanted into the tissue by the needle. After 14 days of clinical observation, the animals were sacrificed and the tissue response to the local chemotherapy was examined. RESULTS: All the polymers were implanted successfully and no implant migration occurred. Localized tissue fibrous necrosis was achieved in the pancreas, without significant complications. The apoptotic index of the tissue within 1 cm of the focus increased. Biochemical parameters were normal in all the dogs. CONCLUSIONS: EUS-guided implantation of polymers is a safe, simple, and minimally invasive technique for interstitial chemotherapy in the pancreas.
Descriptors: antimetabolites, antineoplastic administration and dosage, endosonography, fluorouracil administration and dosage, pancreas ultrasonography, dogs, feasibility studies, injections, intralesional, models, animal, pancreas pathology, polymers administration and dosage.

Trott, D.J., L.J. Filippich, J.C. Bensink, M.T. Downs, S.E. Mckenzie, K.M. Townsend, S.M. Moss, and J.J.C. Chin (2004). **Canine model for investigating the impact of oral enrofloxacin on commensal coliforms and colonization with multidrug-resistant escherichia coli**. *Journal of Medical Microbiology* 53(5): 439-443. ISSN: 0022-2615.
NAL Call Number: QR1.J62
Abstract: A model was developed in dogs to determine the impact of oral enrofloxacin administration on the indigenous coliform population in the gastrointestinal tract and subsequent disposition to colonization by a strain of multidrug-resistant Escherichia coli (MDREC). Dogs given a daily oral dose of 5 mg enrofloxacin kg-1 for 21 consecutive days showed a significant decline in faecal coliforms to levels below detectable limits by 72 In of

administration. Subsequently, faecal coliforms remained suppressed throughout the period of enrofloxacin dosing. Upon termination of antibiotic administration, the number of excreted faecal coliforms slowly returned over an 8-day period, to levels comparable to those seen prior to antibiotic treatment. Enrofloxacin-treated dogs were more effectively colonized by MDREC, evidenced by a significantly increased count of MDREC in the faeces (7.1 +/- 1.5 log10 g-1) compared with non-antibiotic-treated dogs (5.2 +/- 1.2; P = 0.003). Furthermore, antibiotic treatment also sustained a significantly longer period of MDREC excretion in the faeces (26.8 +/- 10.5 days) compared with animals not treated with enrofloxacin (8.5 +/- 5.4 days; P = 0.0215). These results confirm the importance of sustained delivery of an antimicrobial agent to maintain and expand the colonization potential of drug-resistant bacteria in vivo, achieved in part by reducing the competing commensal coliforms in the gastrointestinal tract to below detectable levels in the faeces. Without in vivo antimicrobial selection pressure, commensal coliforms dominated the gastrointestinal tract at the expense of the MDREC population. Conceivably, the model developed could be used to test the efficacy of novel non-antibiotic strategies aimed at monitoring and controlling gastrointestinal colonization by multidrug-resistant members of the Enterobacteriaceae that cause nosocomial infections.
Descriptors: digestive system, ingestion and assimilation, infection, pharmacology, antibacterial therapy, clinical techniques, therapeutic and prophylactic techniques, oral drug therapy, clinical techniques, therapeutic and prophylactic techniques, bacterial colonization, medical microbiology, methodology, nosocomial infections.

Tsuji, Y., H. Yoshimura, F. Uto, T. Tamamoto, I. Asakawa, N. Horikawa, S. Fukugami, H. Sakaguchi, T. Yoshioka, K. Kichikawa, and H. Ohishi (2003). **The influence of the metallic stent for irradiation: experimental study by phantom and normal bile duct of dogs.** *International Journal of Radiation Oncology Biology Physics* 57(2 Supplement): S424. ISSN: 0360-3016.
NAL Call Number: RC271.R3
Descriptors: digestive system, ingestion and assimilation, methods and techniques, radiation biology, histological examination, histology and cytology techniques, laboratory techniques, irradiation, applied and field techniques, metallic stent, medical equipment, phantom experiment, applied and field techniques, dosimetry.

Tsunoda, Y., H. Yao, J. Park, and C. Owyang (2003). **Cholecystokinin synthesizes and secretes leptin in isolated canine gastric chief cells.** *Biochemical and Biophysical Research Communications* 310(3): 681-684. ISSN: 0006-291X.
NAL Call Number: 442.8 B5236
Abstract: It is well recognized that a product of obese (ob) locus and body weight control hormone, leptin, acts on both short-term satiety for meal-induced termination of food intake (gastric phase) and long-term satiety for energy expenditure via the hypothalamus. The considerable sources of leptin are chief cells for gastric phase and adipocytes for the long-term satiety. The objective of this study was to demonstrate if CCK enhances leptin synthesis and secretion in isolated canine gastric chief cells. Confocal immunofluorescence studies showed that the CCK-A receptor and leptin were colocalized in the endoplasm. Western blotting demonstrated that canine chief cells expressed the leptin peptide and its protein level was enhanced by CCK treatment. An ELISA further showed that CCK dose-dependently secreted leptin from isolated canine chief cells. This was reproduced by the high-affinity

CCK-A receptor agonist, CCK-OPE. These results indicate that canine chief cells synthesize and secrete leptin in response to CCK via the high-affinity state of the CCK-A receptor.
Descriptors: cell biology, digestive system, ingestion and assimilation, endocrine system, chemical coordination and homeostasis, metabolism, energy expenditure.

Ueno, T. and J.D.Z. Chen (2004). **Vomiting and gastric electrical dysrhythmia in dogs**. *Scandinavian Journal of Gastroenterology* 39(4): 344-352. ISSN: 0036-5521.
Abstract: Background: The correlation between gastric myoelectrical activity (GMA) and gastrointestinal symptoms such as nausea and vomiting is poorly understood. The aim of this study was to assess the association of GMA with vomiting induced by retrograde gastric electrical stimulation or duodenal balloon distention. Methods: Ten dogs were involved in this study. Vomiting was induced by retrograde gastric electrical stimulation in 6 dogs and by duodenal balloon distention in 4 dogs. Computerized spectral analysis and visual analysis were applied to detect the GMA change during various periods before and after vomiting. Results: Gastric dysrhythmia preceded vomiting but was of brief duration. The major pattern of dysrhythmia immediately before vomiting was tachyarrhythmia and gastric slow wave was completely uncoupled before vomiting. Gastric dysrhythmia and slow wave uncoupling were also noticed immediately after vomiting but the dogs recovered quickly. The major pattern of dysrhythmia after vomiting was arrhythmia. GMA was normal during the periods other than 5 min before and during vomiting and 5 min after vomiting. Conclusions: Gastric dysrhythmia seems to be the cause of vomiting induced by retrograde gastric electrical stimulation or duodenal balloon distention. It is brief and characterized with tachyarrhythmia and uncoupling.
Descriptors: cardiovascular system, transport and circulation, digestive system, ingestion and assimilation, veterinary medicine, medical sciences, arrhythmia, heart disease, gastirc electrical dysrhythmia, digestive system disease, vascular disease, nausea, symptom, tachyarrhythmia, vomiting, computerized spectral analysis, laboratory techniques, spectrum analysis techniques, duodenal balloon distention, experimental surgical techniques, electrogastrography, clinical techniques, diagnostic techniques, retrograde gastric electrical stimulation, gastric myoelectrical activity, gastrointestinal motility.

Vastyan, A.M., A.B. Pinter, A.P. Farkas, P. Vajda, J. Lantos, G. Mehes, and E. Roth (2003). **Seromuscular gastrocystoplasty in dogs.** *Urologia Internationalis* 71(2): 215-218. ISSN: 0042-1138.
Abstract: Introduction: The aim of this study was to investigate the feasibility of seromuscular gastrocystoplasty (SGCP) in an animal model and to compare it to conventional gastrocystoplasty (CGCP). Materials and Methods: CGCP and SGCP (using gastric segments without mucosa) were each performed in 6 dogs. In both procedures, two-thirds of the dome of the bladder were excised and the gastric segment anastomosed to the bladder remnant. Cystography, cystomanometry, measurements of urine pH, and gross and microscopic pathological studies were carried out preoperatively, and postoperatively, at 6 and 12 weeks. Results: All seromuscular gastric segments proved viable, and 6 weeks after the operation they were covered by a thin layer of transitional epithelium, which had gradually thickened by the end of the 12-week follow-up. There was no difference in bladder capacity and compliance between the two groups, however, fasting urinary pH values were higher (less acidic) in the SGCP group. Conclusions: Stripping off the mucosa of the gastric segment

appears to stop hydrochloric acid secretion, thereby lessening the possible risk of ulceration, perforation, dysuria-haematuria, metaplasia and malignancy. The uroepithelium overgrowth of the seromuscular gastric segments might provide a more physiological neo-bladder than when using full-thickness gastrocystoplasty.
Descriptors: digestive system, ingestion and assimilation, methods and techniques, urinary system, chemical coordination and homeostasis, conventional gastrocystoplasty, seromuscular gastrocystoplasty, experimental surgical techniques, laboratory techniques, bladder capacity, urine pH.

Webber, C., C.A. Stokes, S. Persiani, F. Makovec, A. Mcburney, R.P. Kapil, B.A. John, M. D'amato, and L.F. Chasseaud (2004). **Absorption, distribution, metabolism and excretion of the cholecystokinin-1 antagonist dexloxiglumide in the dog**. *European Journal of Drug Metabolism and Pharmacokinetics* 29(1): 15-23. ISSN: 0378-7966.
NAL Call Number: RM301.E8
Abstract: Single oral doses of 14C-dexloxiglumide were rapidly and extensively absorbed in dogs and also eliminated rapidly with a short half-life. Following single intravenous doses, dexloxiglumide was characterised as a drug having a high clearance (30.7 and 27.0 ml/min/kg in males and females respectively), a low volume of distribution (Vss, 0.34 and 0.27 L/kg in males and females respectively) and a moderate systemic availability (about 33%). It was extensively bound to plasma proteins (89%). Dexloxiglumide is mainly cleared by the liver. Its renal clearance was minor. In only the kidney, liver and gastrointestinal tract, were concentrations of 14C generally greater than those in plasma. 14C concentrations generally peaked at 0.25h and declined rapidly during 24h being present only in a few tissues (such as the kidney, liver and gastrointestinal tract) at 24h. Single intravenous or oral doses were mainly excreted in the faeces (77-89%), mostly during 24h. Urine contained up to 7.5% dose. Mean recoveries during 7 days ranged between 93-97%. Biliary excretion of 14C was prominent (64% dose during 24h) in the disposition of 14C which was probably also subjected to some limited enterohepatic circulation. Unchanged dexloxiglumide was the major component in plasma. Urine and faeces contained several 14C-components amongst which unchanged dexloxiglumide was the most important (eg. about 55% dose in faeces). LC-MS/MS of urine and bile extracts showed that dexloxiglumide was metabolised mainly by O-demethylation and by conjugation with glucuronic acid.
Descriptors: digestive system, ingestion and assimilation, metabolism, pharmacology, constipation, digestive system disease, irritable bowel syndrome, liquid chromatography mass spectrometry, chromatographic techniques, laboratory techniques, spectrum analysis techniques, drug absorption, drug distribution, drug metabolism.

Wijk, H.v., P. Fenn, A. Booth, L. Forsyth, and M. Wight (2004). **The development of a recovery bile duct cannulation technique in dogs**. *Animal Technology and Welfare.* 3(3): 199-200. ISSN: 0264-4754.
NAL Call Number: QL55.I5
Abstract: The use of surgical models can provide valuable information on new drug candidates. However, the collection of bile from dogs under terminal anaesthesia has many disadvantages, such as post-surgical trauma, the influence of anaesthesia on gastrointestinal motility and hepatic metabolism and the depletion of bile acids. This article describes a

recovery model in dog that enables the use of a physiologically normal animal for bile collection. The model was developed from the methodology reported by Kissinger et. al (1998). In this model, the common bile duct is cannulated with a T-piece catheter between the last hepatic duct and the entrance to the duodenum. A balloon at the end of the cannula is inflated to divert bile flow into the proximal cannula for collection via the access port. The model has been refined to allow re-infusion of bile salts from outside the cage directly into the access port connected to the distal cannula.

Descriptors: animal experiments, bile, bile ducts, cannulae, cannulation, collection, laboratory animals, methodology, techniques, dogs.

Wikesjo, U.M.E., W.H. Lim, R.C. Thomson, A.D. Cook, J.M. Wozney, and W.R. Hardwick (2003). **Periodontal repair in dogs: evaluation of a bioabsorbable space-providing macroporous membrane with recombinant human bone morphogenetic protein-2.** *Journal of Periodontology* 74(5): 635-647. ISSN: 0022-3492.

Abstract: Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) technologies have been shown to significantly support alveolar bone formation. Biomaterial limitations, however, have restricted the biologic potential for onlay indications. The objective of this study was to evaluate regeneration of alveolar bone and periodontal attachment, and biomaterials reaction following surgical implantation of a space-providing, bioabsorbable, macroporous, polyglycolic acid-trimethylene carbonate (PGA-TMC) membrane combined with a rhBMP-2 construct in a discriminating onlay defect model. Methods: Routine supraalveolar periodontal defects were created at the mandibular premolar teeth in 9 beagle dogs. Contralateral jaw quadrants in subsequent animals were randomly assigned to receive the dome-shaped PGA-TMC (100 to 120 mum pores) membrane with rhBMP-2 (0.2 mg/mL) in a bioresorbable hyaluronan (Hy) carrier or the PGA-TMC membrane with Hy alone (control). The gingival flaps were advanced to submerge the membranes and teeth and sutured. Animals were euthanized at 8 and 24 weeks postsurgery for histologic observations. Results: Jaw quadrants receiving the PGA-TMC membrane alone experienced exposures at various time points throughout the study. Jaw quadrants receiving the PGA-TMC/rhBMP-2 combination remained intact, although one site experienced a late minor exposure. Newly formed alveolar bone approached and became incorporated into the macroporous PGA-TMC membrane in sites receiving rhBMP-2. The PGA-TMC biomaterial was occasionally associated with a limited inflammatory reaction. Residual PGA-TMC could not be observed at 24 weeks postsurgery. Residual Hy could not be observed at any time interval. Regeneration of alveolar bone height (means+-SD) was significantly increased in sites receiving the PGA-TMC/rhBMP 2 combination compared to control (3.8+-1.3 versus 0.7+-0.5 mm at 8 weeks and 4.6+-0.8 versus 2.1+-0.4 mm at 24 weeks; P<0.05). Limited cementum regeneration was observed for PGA-TMC/rhBMP-2 and PGA-TMC control sites. Ankylosis compromised regeneration in sites receiving PGA-TMC/rhBMP-2. Conclusions: The bioabsorbable, space-providing, macroporous PGA-TMC membrane appears to be a compatible biomaterial for bone augmentation procedures. rhBMP-2 significantly enhances alveolar bone augmentation and soft tissue healing when combined with the PGA-TMC membrane.

Descriptors: dental and oral system, ingestion and assimilation, pharmacology, skeletal system, movement and support, ankylosis, joint disease, alveolar ridge augmentation,

experimental surgical techniques, laboratory techniques, bioresorbable hyaluronan carrier, prosthetic, periodontal repair, clinical techniques, polyglycolic acid trimethylene carbonate membrane, prosthetic, surgical implantation, clinical techniques, therapeutic and prophylactic techniques, bone regeneration, cementum regeneration, inflammatory reaction, macroporous, soft tissue healing, space providing, supraalveolar periodontal defects, wound healing.

Willis, S., F. Holzl, B. Wein, A. Tittel, and V. Schumpelick (2007). **Defecation mechanisms after anterior resection with J-pouch-anal and side-to-end anastomosis in dogs.** *International Journal of Colorectal Disease* 22(2): 161-5. ISSN: 0179-1958.
NAL Call Number: RC860
Abstract: BACKGROUND: Colonic J-pouch-anal anastomosis or colonic side-to-end anastomosis is the reconstruction of choice after low anterior resection. However, the mechanisms of defecation after both reconstruction forms are still speculative. METHODS: Low anterior rectal resections were performed in 12 dogs with six colonic J-pouch-anal (pouch) and six coloanal side-to-end (SE) reconstructions. Four months postoperative stool frequency, intestinal transit time, and neorectal compliance were determined by radiography and barostat. Defecation mechanisms were evaluated radiographically during expulsion of artificial stool. RESULTS: One dog with pouch reconstruction could not be evaluated due to an anastomotic leak, while the others had uncomplicated course. Spontaneous stool frequency was significantly increased with both reconstruction methods (control 2.0+/-0.9, pouch 2.7+/-1.2, SE 3.3+/-0.9 day; $p<0.05$). Intestinal transit time was significantly higher with pouch reconstruction due to storage of stool in the pouch and the descending colon compared to SE (control 760+/-82, pouch 592+/-97, SE 550+/-87 min; $p<0.05$). Compliance and functional capacity were higher in pouch than in side-to-end reconstructions (pouch 5.0+/-0.7 ml/mmHg, 124+/-23 ml; SE 2.7+/-0.3 ml/mmHg, 92+/-24 ml; $p<0.05$). During defecation, there were no contractions of the pouch detectable. CONCLUSIONS: The colonic J-pouch reconstruction results in better functional outcome than side-to-end coloanal anastomosis. Our results show that pouch evacuation is passive and independent from pouch motility. The functional principle of the colonic J-pouch is not its reservoir function but a delay of colonic motility.
Descriptors: anal canal surgery, colon surgery, colonic pouches physiology, defecation physiology, proctocolectomy, restorative methods, colectomy, dogs, models, animal.

Xing, J. and J. Chen (2003). **Reproducibility of gastric tone, compliance and postprandial gastric accommodation assessed with barostat in dogs.** In: *Digestive Disease Week and Itinerary Planner 2003, Orlando, FL, USA; May 17-22, 2003,* Abstract No. W1479.
Abstract: Electronic barostat is frequently used to evaluate gastric tone, compliance and visceral perception. These functions can be modulated by daily variations and gastric contractions, and the reproducibility of these tests remains unclear. Aim: to assess the intra- and inter-day reproducibility of measurement of gastric tone, compliance and gastric accommodation with barostat in an animal model. Methods: 10 healthy dogs (17-25 kg) were operated and a gastric cannula was implanted in the anterior stomach. Following experiments were conducted in overnight fasted conscious animals: 1) Inter-day gastric tone (30 min) and compliance: 3 sessions tested at the same time of 3 separate days; 2) Intra-day gastric tone

(30 min) and compliance: 2 sessions tested in the same day separated by a 30 min interval; 3) Inter-day gastric accommodation: 2 sessions performed on two separate days. Fasting gastric tone (30 min) was recorded first, and continued for 1 hour after ingestion of a liquid meal (Boost 237 ml). A barostat system was used. A balloon (800 ml) attached at the end part of a double-lumen catheter was positioned into the stomach via the cannula. Gastric compliance was evaluated by serial isobaric distention. Gastric tone and accommodation were recorded at operating pressure. Inter-day studies were completed within a period of 2 weeks. Coefficient of Variation (CV) calculated as SD/mean. Mean+-SE, ANOVA or Paired t test, $p<0.05$ for significance. Results: 1) Gastric tone (n=8) on 3 separate days was 73.1+-6.5ml, 94.4+-9.6 ml and 88.6+-20.3 ml, with a CV of 28.2+-4.4% (10.8%-42.5%); Gastric compliance was also comparable among the 3 sessions, no significant difference; 2) Gastric tone measured on the same day (n=5) was 68.0+-14.8 ml and 65.5+-15.5 ml (p=0.782), with a mean CV of 22.2+-8.0% (1.21%-42.2%); Gastric compliance (n=5) was comparable between the two sessions. 3) Gastric accommodation (n=5): the mean 1 h postprandial gastric volume was similar: 385.5+-55.7 ml vs. 399.6+-98.4 ml, p=0.539, with a CV of 8.8+-4.6% (1.6%-26.7%). Conclusions: Inter- and intra-day gastric tone and compliance and Inter-day gastric accommodation were relatively reproducible in most animals when tested under the same experimental conditions (timing, etc). However, considerable variations may occur in fasting gastric tone and compliance measurement in certain individuals and cautions should be given when interpreting related results.

Descriptors: digestive system, ingestion and assimilation, methods and techniques, barostat method, laboratory techniques, gastric compliance, gastric tone, modulation, postprandial gastric accommodation.

Endocrine System

Bailhache, E., K. Ouguerram, C. Gayet, M. Krempf, B. Siliart, T. Magot, and P. Nguyen (2003). **An insulin-resistant hypertriglyceridaemic normotensive obese dog model: assessment of insulin resistance by the euglycaemic hyperinsulinaemic clamp in combination with the stable isotope technique.** *Journal of Animal Physiology and Animal Nutrition* 87(3-4): 86-95. ISSN: 0931-2439.

NAL Call Number: 389.78 Z3

Abstract: Many studies have shown that in humans insulin resistance (IR) is associated with obesity and hypertriglyceridaemia. The aim of our study was to develop slowly dietary-induced obesity in dogs through long-term overfeeding of a high-fat diet, and to characterize this IR, hypertriglyceridaemic and normotensive model. Insulin resistance was assessed by the euglycaemic hyperinsulinaemic clamp technique. The contribution of hepatic glucose production during the clamp was evaluated using a constant stable-isotope-labelled glucose infusion. Overfeeding a high-fat diet for 7 months was associated with a 43+-5% body weight increase. Insulin resistance was characterized by hyperinsulinaemia in the unfed state (10+-1 vs. 24+-1 muU/ml, in healthy and obese dogs, respectively, p<0.02) and by a reduction of the insulin-mediated glucose uptake (28+-3 vs. 16+-1 mg/kg/min, p<0.02). Hepatic glucose production suppression under insulin infusion allowed to conclude that this reduced glucose uptake resulted from a decrease of insulin sensitivity in obese dogs. Furthermore, animals remained normotensive and exhibited a marked hypertriglyceridaemia (0.26+-0.04 vs. 0.76+-0.15 mmol/l, in healthy and obese dogs, respectively, p<0.02). Because hypertriglyceridaemia is the most common lipid abnormality in insulin-resistant humans, this dog with slowly induced obesity may constitute a good model to study the consequences of IR in lipid metabolism independently of vascular changes.

Descriptors: endocrine system, metabolism, nutrition, hypertriglyceridemia, insulin resistance, obesity, nutritional disease, euglycemic hyperinsulinemic clamp technique, laboratory techniques, high fat diet, applied and field techniques.

Costa, M.J., Y. Song, P. Macours, C. Massart, M.C. Many, S. Costagliola, J.E. Dumont, J. Van Sande, and V. Vanvooren (2004). **Sphingolipid-cholesterol domains (lipid rafts) in normal human and dog thyroid follicular cells are not involved in thyrotropin receptor signaling.** *Endocrinology* 145(3): 1464-1472. ISSN: 0013-7227.

NAL Call Number: 448.8 EN2

Abstract: Partition of signaling molecules in sphingolipid-cholesterol-enriched membrane domains, among which are the caveolae, may contribute to signal transduction efficiency. In normal thyroid, nothing is known about a putative TSH/cAMP cascade compartmentation in caveolae or other sphingolipid-cholesterol-enriched membrane domains. In this study we show for the first time that caveolae are present in the apical membrane of dog and human thyrocytes: caveolin-1 mRNA presence is demonstrated by Northern blotting in primary cultures and that of the caveolin-1 protein by immunohistochemistry performed on human thyroid tissue. The TSH receptor located in the basal membrane can therefore

not be located in caveolae. We demonstrate for the first time by biochemical methods the existence of sphingolipid-cholesterol-enriched domains in human and dog thyroid follicular cells that contain caveolin, flotillin-2, and the insulin receptor. We assessed a possible sphingolipid-cholesterol-enriched domains compartmentation of the TSH receptor and the alpha-subunit of the heterotrimeric Gs and Gq proteins using two approaches: Western blotting on detergent-resistant membranes isolated from thyrocytes in primary cultures and the influence of 10 mM methyl-beta-cyclodextrin, a cholesterol chelator, on basal and stimulated cAMP accumulation in intact thyrocytes. The results from both types of experiments strongly suggest that the TSH/cAMP cascade in thyroid cells is not associated with sphingolipid-cholesterol-enriched membrane domains.
Descriptors: biochemistry and molecular biophysics, endocrine system, chemical coordination and homeostasis, northern blot, genetic techniques, laboratory techniques, signal transduction efficiency.

Critchley, L., B. Ding, B. Fok, D. Wang, B. Tomlinson, A. James, G.N. Thomas, and J. Critchley (2004). **The effects of candesartan and ramipril on adrenal catecholamine release in anaesthetized dogs**. *European Journal of Pharmacology* 489(1-2): 67-75. ISSN: 0014-2999.
NAL Call Number: QP901.E8
Descriptors: angiotensin II type 1 receptor antagonist, angiotensin II converting enzyme inhibitor ramipril, endocrine system, chemical coordination and homeostasis, pharmacology, blood pressure.

Fosgerau, K., S.D. Mittelman, A. Sunehag, M.K. Dea, K. Lundgren, and R.N. Bergman (2001). **Lack of hepatic "interregulation" during inhibition of glycogenolysis in a canine model**. *American Journal of Physiology* 281(2 Part 1): E375-E383. ISSN: 0002-9513.
NAL Call Number: 447.8 Am3
Abstract: It has been proposed that the glycogenolytic and gluconeogenic pathways contributing to endogenous glucose production are interrelated. Thus a change in one source of glucose 6-phosphate might be compensated for by an inverse change in the other pathway. We therefore investigated the effects of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB), a potent glycogen phosphorylase inhibitor, on glucose production in fasted conscious dogs. When dogs were treated acutely with high glucagon, glucose production rose from 1.93+-0.14 to 3.07+-0.37 mgcntdotkg-1cntdotmin-1 (P<0.01). When dogs were treated acutely with DAB in addition to high glucagon infusion, the stimulation of the glycogenolytic rate was completely suppressed. Glucose production rose from 1.85+-0.20 to 2.41+-0.17 mgcntdotkg-1cntdotmin-1 (P<0.05), which was due to the increase in gluconeogenesis from 0.93+-0.09 to 1.54+-0.08 mgcntdotkg-1cntdotmin-1 (P<0.001). In conclusion, infusion of DAB inhibited glycogenolysis; however, the absolute contribution of gluconeogenesis to glucose production was not affected. These results suggest that inhibition of glycogenolysis could be an effective antidiabetic treatment.
Descriptors: endocrine system, type 2 diabetes, non insulin dependent, endocrine disease, pancreas, metabolic disease, treatment , gluconeogenesis, glycogenolysis, inhibition, hepatic interregulation.

Furukawa, N., M. Hatano, and E. Nakamura (2003). **Antro-pancreatic reflexes: long- and short-route reflexes in exocrine and endocrine pancreatic secretion in dogs.** *Autonomic Neuroscience Basic and Clinical* 106(2): 110-118. ISSN: 1566-0702.

Abstract: Pancreatic exocrine secretion is known to be facilitated by gastric antral distension via long- and short-route reflexes. In this study, we studied the effects of gastric distension on intra-pancreatic nerve discharges and blood insulin level as well as pancreatic exocrine secretion. Mongrel dogs were anesthetized with ketamine and thiopental, and immediately decerebrated. This study consisted of two series of experiments. In the first series, efferent discharges in an intra-pancreatic nerve branch were recorded, and its responses to antral distension were analyzed. In the second series, effects of antral distension on pancreatic exocrine secretion and blood insulin level were observed before and after vagotomy in splanchnicectomized dogs. Efferent discharges in a pancreatic nerve branch were increased by antral distension. Neither vagotomy nor splanchnicectomy produced obvious changes in the neural response. In splanchnicectomized dogs, antral distension elevated blood insulin level and increased pancreatic exocrine secretion. After subsequent vagotomy, these effects were reduced, but the increases were still greater than 50%. These results indicate that the antro-pancreatic short-route reflex plays a significant role in exocrine secretion, and also suggest that insulin release is increased by antral distension independent of blood glucose level.

Descriptors: endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, splanchnicectomy, experimental surgical techniques, laboratory techniques, vagotomy, antro pancreatic reflexes, gastric distension.

Gayet, C., B. Siliart, H. Shibata, T. Honjoh, M. Saito, and P. Nguyen (2004). **Adiponectin and leptin: early markers of insulin resistance (ir) in a canine model of obesity**. *International Journal of Obesity* 28(Suppl. 1): S168. ISSN: 0307-0565.

NAL Call Number: RC628.A1O2

Descriptors: metabolism, endocrine system, obesity, nutritional disease, insulin resistance, endocrine disease, pancreas, metabolic disease, disease progression, body weight, insulin sensitivity, glucose infusion rate.

Notes: Meeting Information: 13th European Congress on Obesity, Prague, Czech Republic; May 26 -29, 2004.

Gustavson, S.M., M. Nishizawa, B. Farmer, D. Neal, M. Brissova, A.C. Powers, and A.D. Cherrington (2003). **A fall in portal vein insulin does not cause the alpha-cell response to mild, non-insulin-induced hypoglycemia in conscious dogs.** *Metabolism Clinical and Experimental* 52(11): 1418-1425. ISSN: 0026-0495.

NAL Call Number: 448.8 M56

Abstract: The aim of the present study was to determine whether a decrease in the portal vein insulin level during non-insulin-induced hypoglycemia is sensed and is responsible for the normal increase in glucagon release from the alpha cell. To address this aim, a glycogen phosphorylase inhibitor was used to create mild, non-insulin-induced hypoglycemia in 2 groups of 18-hour fasted conscious dogs. Arterial insulin was clamped at a basal level in both groups, but in one group (PE) the portal vein insulin level was permitted to fall by approximately 65% while in the other group (POR) it was clamped at a basal level. In both groups

glucose was infused at a variable rate to clamp the plasma glucose level at approximately 70 mg/dL. Plasma glucagon (pg/mL) rose to indistinguishable maxima in both groups (56+-3 in PE and 67+-9 in POR). Likewise, glucagon secretion (pg/kg/min) increased similarly (189+-32 to 455+-203 in PE and 192+-50 to 686+-237 in POR). Thus, the increase in glucagon release was not inhibited when the portal vein insulin level was prevented from decreasing (POR group). Clearly, a fall in the portal vein insulin level is not required for a normal alpha-cell response to mild, non-insulin-induced hypoglycemia.
Descriptors: endocrine system, chemical coordination and homeostasis, metabolism, mild non insulin induced hypoglycemia, metabolic disease, alpha cell response.

Harris, G.D., S.J. Vore, K. Salleng, D. Aycock, and C. Yu (2004). **Intracranial pressure (icp) during treatment of a diabetic hyperglycemic canine model: 0.45% Vs. 0.9% Saline**. *Diabetes* 53(Suppl. 2): A421. ISSN: 0012-1797.
NAL Call Number: RC658.A1D5
Descriptors: endocrine system, diabetic ketoacidosis, endocrine disease, pancreas, metabolic disease, diabetic hyperglycemia, drug therapy, drug induced, anesthesia, clinical techniques, hematocrit, clinical techniques, diagnostic techniques, mechanical ventilation, laboratory techniques, pancreatectomy.

Kim, S.P., M. Ellmerer, E.L. Kirkman, and R.N.A.R.A. Bergman (2007). **Beta-cell "rest" accompanies reduced first-pass hepatic insulin extraction in the insulin-resistant, fat-fed canine model**. *American Journal of Physiology: Endocrinology and Metabolism* 292(6): E1581-E1589. ISSN: 0193-1849.
NAL Call Number: 447.8 Am3
Descriptors: biochemistry and molecular biophysics, nutrition, metabolism, endocrine system, hyperinsulinemia, obesity, magnetic resonance imaging, laboratory techniques, diagnostic techniques, clinical techniques, imaging and microscopy techniques, insulin sensitivity, insulin resistance, glucose homeostasis, isocaloric diet, fat, diet, physiological mechanism, first pass hepatic insulin extraction.

Lamouche, S. and N. Yamaguchi (2003). **PACAP release from the canine adrenal gland in vivo: its functional role in severe hypotension.** *American Journal of Physiology* 284(2 Part 2): R588-R597. ISSN: 0002-9513.
NAL Call Number: 447.8 Am3
Abstract: This study was to investigate if endogenous pituitary adenylate cyclase-activating polypeptide (PACAP) can be released during direct splanchnic nerve stimulation in vivo and to determine whether PACAP in the adrenal gland can modulate the medullary response to sympathoadrenal reflex. The output of adrenal catecholamine and PACAP-38-like immunoreactivity (PACAP-38-ir) increased in a frequency-dependent manner after direct splanchnic nerve stimulation (0.2-20 Hz). Both responses were highly reproducible, and PACAP-38-ir output closely correlated with catecholamine output. Sodium nitroprusside (SNP; 0.1 mg/kg iv bolus) caused a severe hypotension resulting in marked increases in catecholamine secretion. In the presence of local PACAP-27 (125 ng), the maximum catecholamine response to SNP was significantly potentiated in a synergistic manner compared with that obtained in

the group receiving SNP or PACAP-27 alone. The study indicates that endogenous PACAP-38 can be released particularly when the sympathoadrenal system is highly activated and that the local exogenous PACAP-27 enhanced the reflex-induced catecholamine release, suggesting collectively a facilitating role of PACAP as neuromodulator in the sympathoadrenal function in vivo.
Descriptors: endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, hypotension,vascular disease, sympathoadrenal reflex.

Lantinga Van Leeuwen, I.S., J.A. Mol, H.S. Kooistra, A. Rijnberk, M. Breen, C. Renier, and B.A. Van Oost (2000). **Cloning of the canine gene encoding transcription factor pit-1 and its exclusion as candidate gene in a canine model of pituitary dwarfism**. *Mammalian Genome* 11(1): 31-36. ISSN: 0938-8990.
NAL Call Number: QL738.5.M359
Abstract: Combined pituitary hormone deficiency (CPHD) is an autosomal recessive inherited disease of German shepherd dogs characterized primarily by dwarfism. In mice and humans a similar genetic disorder has been described that results from an alteration in the gene encoding the transcription factor Pit-1. In this study we characterized the canine Pit-1 gene, determined the chromosomal localization of the Pit-1 gene, and screened dwarf German shepherd dogs for the presence of mutations in this gene. The full-length canine Pit-1 cDNA contained an open reading frame encoding 291 amino acids, 92 bp of 5'-untranslated region, and 1959 bp of 3'-untranslated region. The deduced amino acid sequence was highly homologous with Pit-1 of other mammalian species. Using a Pit-1 BAC clone as probe, the Pit-1 gene was mapped by FISH to canine Chromosome (Chr) 31. In dwarf German shepherd dogs a C to A transversion was detected, causing a Phe (TTC) to Leu (TTA) substitution at codon 81. This alteration was present neither in other canine breeds analyzed nor in other mammalian species. However, healthy German shepherd dogs were also homozygous for the mutant allele, indicating that it is not the primary disease-causing mutation. In addition, linkage analysis of polymorphic DNA markers flanking the Pit-1 gene, 41K19 and 52L05, revealed no co-segregation between the Pit-1 locus and the CPHD phenotype. These findings suggest that a gene other than Pit-1 is responsible for the pituitary anomaly in dwarf German shepherd dogs.
Descriptors: molecular genetics, endocrine system, chemical coordination and homeostasis, pituitary dwarfism, bone disease, amino acid sequence, chromosome 31.

Lavine, S.J. and P. Prcevski (2007). **Effect of glycemic control in a canine model of diabetes and left ventricular dysfunction on left ventricular performance: utility of the index of myocardial performance**. *Journal of the American College of Cardiology* 49(9, Suppl. A): 62A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: metabolism, endocrine system, diabetes, left ventricular dysfunction, heart disease, diabetic cardiomyopathy, glycemic control.
Notes: Meeting Information: 56th Annual Scientific Session of the American College of Cardiology, New Orleans, LA, USA; March 24 -27, 2007.

Lee, T.M., M.S. Lin, T.F. Chou, C.H. Tsai, and N.C. Chang (2004). **Adjunctive 17beta-estradiol administration reduces infarct size by altered expression of canine myocardial connexin43 protein**. *Cardiovascular Research* 63(1): 109-117. ISSN: 0008-6363.
NAL Call Number: QM178.A1C38
Descriptors: cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, pharmacology, coronary occlusion, heart disease, ischemia, vascular disease, ischemia reperfusion injury, myocardial infarction, western blot, genetic techniques, confocal microscopy, imaging and microscopy techniques, lucigenin derived chemiluminescence, laboratory techniques, infarct size.

Liberty, I.F., V. Ionut, S.P. Kim, M. Ader, M. Lottati, and R.N. Bergman (2005). **Hiv-protease inhibitor treatment, a new canine experimental model of insulin resistance.** *Journal of Investigative Medicine* 53(1, Suppl. S): S106-S107. ISSN: 1081-5589.
NAL Call Number: R11.C5
Descriptors: endocrine system, chemical coordination and homeostasis, insulin resistance, metabolic disease, endocrine disease, insulin sensitivity.
Notes: Meeting Information: Western Student Medical Research Forum held in conjunction with the Western Section of the American Federation for Medical Research/Western Society for Clinical Investigation/Western Association of Physicians/Western Society for Pediatric Research, Carmel, CA, USA; February 3-5, 2005.

Mraovic, B.A., F.A. Kehl, P.S. Pagel, D.C. Warltier, and J.R. Kersten (2002). **Hyperglycemia attenuates coronary collateral development in a canine model of repetitive coronary artery occlusion.** *Anesthesiology Abstracts of Scientific Papers Annual Meeting*(2001): Abstract No. A-635.
Descriptors: anesthesiology, medical sciences, cardiovascular medicine, clinical endocrinology, human medicine, pharmacology, diabetes mellitus, endocrine disease, pancreas, metabolic disease, complications, hyperglycemia , repetitive coronary artery occlusion, heart disease, vascular disease, hemodynamics .
Notes: Meeting Information: 2001 Annual Meeting of the American Society of Anesthesiologists, New Orleans, LA, USA; October 13-17, 2001.

Oktaei, H., M.H. Shokouh Amiri, L. Gaber, O. Gaber, A. Salem, and A.E. Kitabchi (2005). **The effect of chronic hyperinsulinemia on coronary arteries in nontransplant dog model.** *Journal of Investigative Medicine* 53(1, Suppl. S): S322. ISSN: 1081-5589.
NAL Call Number: R11.C5
Descriptors: cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, atherosclerosis, vascular disease, chronic hyperinsulinemia, endocrine disease, pancreas, endocrine disease, risk factor.
Notes: Meeting Information: Western Student Medical Research Forum held in conjunction with the Western Section of the American Federation for Medical Research/Western Society for Clinical Investigation/Western Association of Physicians/Western Society for Pediatric Research, Carmel, CA, USA; February 3-5, 2005.

Oktaei, H., S.A. Hosein, G. Osama, B.A. Michael, A. Salem, and A. Kitabch (2003). **The effect of surgical menopause on lipid and carbohydrate metabolism, in six years model of hyperinsulinemia in dogs.** *Diabetes* 52(Supplement 1): A293. ISSN: 0012-1797.
NAL Call Number: RC658.A1D5
Descriptors: endocrine system, chemical coordination and homeostasis, metabolism, hyperinsulinemia , endocrine disease, pancreas, metabolic disease, ovariectomy, experimental surgical techniques, laboratory techniques, menopause.
Notes: Meeting Information: 63rd Scientific Sessions of the American Diabetes Association, New Orleans, LA, USA; June 13-17, 2003.

Okuda, Y., J. Pena, J. Chou, and J.B. Field (2001). **Acute effects of growth hormone on metabolism of pancreatic hormones, glucose and ketone bodies.** *Diabetes Research and Clinical Practice* 53(1): 1-8. ISSN: 0168-8227.
Abstract: Controversy exists as to whether acute administration of growth hormone has insulin-like effects. In conscious dogs, acute effects on plasma flows, plasma glucose, hepatic glucose output, free fatty acids, ketone bodies, insulin, and glucagon were determined following intravenous injection of 1 mg of growth hormone extracted from the canine pituitary gland. The following results were obtained: (1) Plasma flows in the portal vein, hepatic artery and hepatic vein were significantly increased 20 min after growth hormone administration. (2) By 40 min after growth hormone, the glucose concentration in these three vessels was significantly increased. (3) Hepatic glucose output was significantly increased 60 min after growth hormone administration. (4) Free fatty acids levels were significantly but transiently increased at 20 min, while ketone body concentrations were elevated at 120-180 min. (5) The insulin levels in the three vessels demonstrated a biphasic response. In the portal vein, they were significantly higher 20 min after growth hormone and again at 150-180 min. Glucagon concentrations were increased in all three vessels by 20 min and remained elevated for the remainder of the experiment. These results do not support an acute insulin-like action of growth hormone in normal dogs.
Descriptors: animal model, growth hormone, insulin-like effects, plasma glucose, glucagon.

Ozaki, K.I., K. Yogo, H. Sudo, H. Muramatsu, K. Kamei, Y. Kawabe, Z. Itoh, S. Omura, and H. Takanashi (2007). **Mitemcinal (gm-611), an orally active motilin receptor agonist, accelerates gastric emptying in a diabetic gastroparesis dog model**. *Gastroenterology* 132(4, Suppl. 2): A685. ISSN: 0016-5085.
Descriptors: pharmacology, nervous system, neural coordination, digestive system, ingestion and assimilation, veterinary medicine, medical sciences, hyperglycemia ,metabolic disease, renal failure, urologic disease, liver failure, digestive system disease, gastroparesis, nervous system disease, digestive system disease, diabetes, endocrine disease, pancreas, toxicity, metabolic disease, drug induced, aap method, laboratory techniques, gastric emptying.
Notes: Meeting Information: Digestive Disease Week Meeting/108th Annual Meeting of the American Gastroenterological Association, Washington, DC, USA; May 19-24, 2007.

Rashid, S., Z.Q. Shi, M. Niwa, J.M.R. Mathoo, M. Vandelangeryt, D. Bilinski, G.F. Lewis, and M. Vranic (2000). **Beta-blockade, but not normoglycemia or hyperinsulinemia, markedly diminishes stress-induced hyperglycemia in diabetic dogs**. *Diabetes* 49(2): 253-262.

ISSN: 0012-1797.
NAL Call Number: RC658.A1D5
Abstract: Stress-induced hyperglycemia can lead to significant deterioration in glycemic control in individuals with diabetes. Previously, we have shown in normal dogs that, after intracerebroventricular (ICV) administration of carbachol (a model of moderate stress), increases in both the metabolic clearance rate (MCR) of glucose and endogenous glucose production (GP) occur. However, in hyperglycemic diabetic dogs subjected to the same stress, the MCR of glucose does not increase and glycemia therefore markedly deteriorates because of stimulation of GP. Our aims were to determine the following: 1) whether insulin-induced acute normalization of glycemia, with or without beta-blockade, would correct glucose clearance and prevent the hyperglycemic effect of stress, and 2) whether hyperinsulinemia per se could correct these abnormalities. Stress was induced by ICV carbachol in 27 experiments in five alloxan-administered diabetic dogs subjected to the following protocols in random order: 1) basal insulin infusion (BI) to restore normoglycemia; 2) basal insulin infusion with beta-blockade (BI+block); 3) normoglycemic-hyperinsulinemic clamp with threefold elevation of insulin above basal (3X BI); and 4) normoglycemic-hyperinsulinemic clamp with fivefold elevation of insulin above basal (5X BI). The BI+block protocol fully prevented stress-induced hyperglycemia, both by increasing MCR (DELTAMCR at peak: 0.72+-0.25 mlcntdotkg-1cntdotmin-1 vs. no change in BI, P<0.05) and by diminishing the stress-induced increment in GP observed in BI (DELTAGP at peak: 3.72+-0.09 mumolcntdotkg-1cntdotmin-1 for BI+block vs. 14.10+-0.31 mumolcntdotkg-1cntdotmin-1 for BI, P<0.0001). In contrast, 3X BI and 5X BI treatments with normoglycemic-hyperinsulinemic clamps proportionately increased basal MCR at baseline, but paradoxically were not associated with an increase in MCR in response to stress, which induced a twofold increase in GP. Thus, in alloxan-administered diabetic dogs, stress increased GP but not MCR, despite normalization of glycemia with basal or high insulin. In contrast, beta-adrenergic blockade almost completely restored the metabolic response to stress to normal and prevented marked hyperglycemia, both by limiting the rise in GP and by increasing glucose MCR. We conclude that acute normalization of glycemia with basal insulin or hyperinsulinemia does not prevent hyperglycemic effects of stress unless accompanied by beta-blockade, and we speculate that short-term beta-blockade may be a useful treatment modality under some stress conditions in patients with diabetes.
Descriptors: behavior, endocrine system, chemical coordination and homeostasis, metabolism, diabetes, endocrine disease, pancreas, metabolic disease, hyperinsulinemia, pancreas, stress induced hyperglycemia, beta blockade therapy, clinical potential, pharmacological method, physiological method, short term, glycemic control, metabolic clearance rate, normoglycemia.

Shackleford, D.M., W.A.F. Faassen, N. Houwing, H. Lass, G.A. Edwards, C.J.H. Porter, and W.N. Charman (2003). **Contribution of lymphatically transported testosterone undecanoate to the systemic exposure of testosterone after oral administration of two andriol formulations in conscious lymph duct-cannulated dogs.** *Journal of Pharmacology and Experimental Therapeutics* 306(3): 925-933. ISSN: 0022-3565.
NAL Call Number: 396.8 J82
Abstract: Orally administered testosterone (T) is ineffective in the treatment of male andro-

gen deficiency syndromes due to extensive presystemic first-pass metabolism. In contrast, the lipophilic long-chain ester testosterone undecanoate (TU) exhibits androgenic activity that has been attributed to formation of T via systemic hydrolysis of lymphatically transported TU. However, there are no definitive data regarding the oral bioavailability of TU or the extent to which lymphatically transported TU contributes to the systemic availability of T after oral TU administration. This report describes the application of stable isotope methodology in a thoracic lymph duct-cannulated dog model to study the oral bioavailability and lymphatic transport of TU after postprandial administration. When administered as either Andriol or Andriol Testocaps, the mean (+-S.E., n=4) absolute bioavailability of TU was 3.25+-0.48 and 2.88+-0.88%, respectively, and lymphatically transported TU accounted for between 91.5 and 99.7% of the systemically available ester. Model-independent pharmacokinetic analysis indicated that 83.6+-1.6 and 84.1+-8.2% of the systemically available T, resulting from Andriol or Andriol Testocaps, respectively, was due to systemic hydrolysis of lymphatically transported TU. These data demonstrate that intestinal lymphatic transport of TU produces increased systemic exposure of T by avoiding the extensive first-pass effect responsible for the inactivation of T after oral administration.
Descriptors: blood and lymphatics, transport and circulation, endocrine system, chemical coordination and homeostasis, pharmacology, androgen deficiency syndrome, reproductive system disease, pharmacokinetic analysis, laboratory techniques.

Sivakumar, A.V.N., V. Leela, S. Viswanathan, and M. Nayeem (2001). **Effect of induced hyperthyroidism by thyroxine injection on cardiovascular function in canine model**. *Indian Veterinary Journal* 78(5): 397-399. ISSN: 0019-6479.
NAL Call Number: 41.8 IN2
Abstract: Experimental hyperthyroidism was produced in dogs by L-thyroxine injection and it was observed that most of the segments of ECG were increased and both the B.P. and heart rate were found to be increased. Hence care must be taken to regulate the dosage of thyroxine in substitution therapy in clinical cases of hypothyroidism.
Descriptors: cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, pharmacology, hyperthyroidism , endocrine disease, thyroid, electrocardiography, analytical method, blood pressure, cardiovascular function, heart rate.

Tashiro, H., H. Iwata, G.L. Warnock, Y. Ikada, and T. Tsuji (1997). **Application of agarose microcapsule to allo-islet transplantation in canine model**. *Acta Diabetologica* 34(2): 103. ISSN: 0940-5429.
NAL Call Number: RC660.A1
Descriptors: endocrine system, chemical coordination and homeostasis, metabolism, physiology, agarose microcapsule, animal model, bioartificial pancreas, diabetes, endocrine disease, pancreas, endocrine system, functional efficacy, independence, insulin, islet allotransplantation, metabolic disease, therapeutic method.
Notes: Meeting Information: 6th Congress of the International Pancreas and Islet Transplant Association (IPITA) 1997, Milan, Italy; September 24-27, 1997.

Tolan, I.A., D. Ragoobirsingh, and E.Y.S.A. Morrison (1997). **In vivo studies of the effects of capsaicin on blood glucose levels and insulin binding using dog models**. *Diabetologia* 40(SUPPL. 1): A243. ISSN: 0012-186X.
NAL Call Number: RC660.A1D52
Descriptors: blood and lymphatics, transport and circulation, endocrine system, chemical coordination and homeostasis, metabolism, pharmacognosy, antidiabetic drug binding, blood levels, capsaicin, diabetes, glucose, pharmacodynamics.
Notes: Meeting Information: 16th International Diabetes Federation Congress, Helsinki, Finland; July 20-25, 1997.

Wu Jian Hui , Sun Zu Yue , Zhong En Hong , Zhu Yan , Liu Gui Ming , He Gui Lin , and Cao Lin (2003). **Pathology changes of vas deferens in benign prostatic hyperplasia model of beagle dogs.** *Zhongguo Yaolixue Yu Dulixue Zazhi* 17(3): 221-226. ISSN: 1000-3002.
Abstract: AIM: The objective of this investigation was to research the proliferation mechanism of vas deferens in benign prostatic hyperplasia. METHODS: The vas deferens, from beagle dogs which have been administered testosterone propionate(TP) to build benign prostatic hyperplasia model in vivo, was analyzed by a series of methods. Dihydrotestosterone (DHT) in vas deferens was detected by radioimmunoassay, the slices (4 mum) of vas deferens were stained with HE, and the duct area as well as the height of epithelial cell were measured with videodensitometer. The apoptosis rate was determined by flow cytometry method. The expression of prostatic specific antigen (PSA), prostatic acid phosphatase (PAP), Bcl-2 and P53 were determined by immunohistochemical methods. The nucleosomal DNA fragmentation was monitored by agarose gel electrophoresis. RESULTS: DHT level of vas deferens was increased with increasing TP doses, but there was no significant difference between groups. After being administered TP, the duct area of vas deferens was enlarged (P<0.01), and the height of epithelial cell was increased (P<0.01). The cell apoptosis rate of control was higher than that of 0.8 and 7.5 mgcntdotkg-1 TP groups(P<0.01). While there were no differences in expression of PSA, PAP and Bcl-2 between control and other groups, the expression of P53 of control was higher than that of the other groups(P<0.05). In agarose gel electrophoresis, the 200 bp base pair DNA fragments and the multiples of them were observed in control, while similar phenomenon didn't find in other groups. CONCLUSION: DHT induces vas deferens to proliferate, and the proliferation of vas deferens is related to inhibition of apoptosis.
Descriptors: endocrine system, chemical coordination and homeostasis, reproductive system, reproduction, tumor biology, benign prostatic hyperplasia, reproductive system disease, male, urologic disease, pathology changes, proliferation mechanism.
Language of Text: Chinese.

Yamaguchi, N., T.R. Minassian, and S. Yamaguchi (2003). **Effects of pacap1-27 on the canine endocrine pancreas in vivo: interaction with cholinergic mechanism.** *Canadian Journal of Physiology and Pharmacology* 81(7): 720-729. ISSN: 0008-4212.
NAL Call Number: 470 C16E
Abstract: The aim of the present study was to characterize the effects of pituitary adenylate cyclase activating polypeptide (PACAP) on the endocrine pancreas in anesthetized dogs. PACAP1-27 and a PACAP receptor (PAC1) blocker, PACAP6-27, were locally administered

to the pancreas. PACAP1-27 (0.005-5 mug) increased basal insulin and glucagon secretion in a dose-dependent manner. PACAP6-27 (200 mug) blocked the glucagon response to PACAP1-27 (0.5 mug) by about 80%, while the insulin response remained unchanged. With a higher dose of PACAP6-27 (500 mug), both responses to PACAP1-27 were inhibited by more than 80%. In the presence of atropine with an equivalent dose (128.2 mug) of PACAP6-27 (500 mug) on a molar basis, the insulin response to PACAP1-27 was diminished by about 20%, while the glucagon response was enhanced by about 80%. The PACAP1-27-induced increase in pancreatic venous blood flow was blocked by PACAP6-27 but not by atropine. The study suggests that the endocrine secretagogue effect of PACAP1-27 is primarily mediated by the PAC1 receptor, and that PACAP1-27 may interact with muscarinic receptor function in PACAP-induced insulin and glucagon secretion in the canine pancreas in vivo.

Descriptors: biochemistry and molecular biophysics, endocrine system, chemical coordination and homeostasis, cholinergic mechanism, pancreatic venous blood flow.

Hemodynamics

Bartoli, C.R., K. Okabe, I. Akiyama, B. Coull, and J.J. Godleski (2008). **Repeat microsphere delivery for serial measurement of regional blood perfusion in the chronically instrumented, conscious canine.** *Journal of Surgical Research* 145(1): 135-41. ISSN: 0022-4804.

Abstract: INTRODUCTION: For chronic, repeat hemodynamic studies in conscious dogs, we designed and tested a chronically instrumented canine microsphere delivery model. The goals of this study were (1) to investigate the accuracy of repeated estimations of blood perfusion using fluorescent-labeled microspheres and (2) to develop and validate a chronic preparation that permits consecutive estimations in the same conscious animal over an extended protocol. METHODS: Via thoracotomy, nine dogs were instrumented with left atrial appendage and aortic vascular access catheters connected to subcutaneous vascular access ports. Four animals received seven serial injections of 1.6 million 15 microm microspheres (total: 11.2 million), and five animals received 8 serial injections of 2.25 million microspheres (total: 18 million) over the course of 11 or 18 wk. RESULTS: All catheters have remained bidirectionally patent during protocol for 14.9 +/- 0.8 (mean +/- SEM) wk. Sphere accumulation did not significantly alter global myocardial (P = 0.69, P = 0.25), renal (P = 0.92, P = 0.12), hepatic (P = 0.84, P = 0.32), or splenic (P = 0.33, P = 0.70) blood perfusion in either set of animals. CONCLUSIONS: Catheters remained bidirectionally patent for months, did not interfere with the hemodynamic responses of the preparation, and allowed repeat percutaneous injection of microspheres and withdrawal of reference arterial blood from within conscious canines. Eight serial injections totaling 18 million microspheres over 18 weeks did not alter regional myocardial, hepatic, renal, or splenic blood flow. This dependable, chronic, percutaneous arterial access preparation provides a means for examining acute and long-term effects of pathophysiological, pharmaceutical, and environmental influences on regional arterial blood flow in conscious, large animals.

Descriptors: arteries physiology, catheters, indwelling, consciousness physiology, infusions, intra arterial methods, microspheres, coronary vessels physiology, dogs, infusions, intra arterial instrumentation, kidney blood supply, liver blood supply, models, animal, regional blood flow physiology, spleen blood supply, time factors.

Boswood, A. and A. Murphy (2006). **The effect of heart disease, heart failure and diuresis on selected laboratory and electrocardiographic parameters in dogs.** *Journal of Veterinary Cardiology* 8(1): 1-9. ISSN: 1760-2734.

NAL Call Number: SF811

Abstract: Objectives: To evaluate the influence of heart disease and heart failure on 9 parameters: the serum sodium, potassium, chloride, creatinine and urea concentrations, heart rate, vaso-vagal tonus index (VVTI), red cell number and hematocrit. Background: Previous studies have demonstrated that heart disease, heart failure and their treatment are associated with changes in laboratory and electrocardiographic parameters. Animals, materials and methods: Data were retrieved from 92 client-owned dogs with naturally occurring heart disease. Dogs were classified according to the severity of their heart disease and or the

presence of heart failure. The effects of heart disease, the progression into heart failure, the initiation of successful therapy and the administration of diuretics on these parameters were determined. Results: Worse heart failure was characterized by the following changes: a significant fall in serum sodium and chloride concentrations and VVTI, and a significant increase in the serum urea concentration and heart rate. The onset of heart failure was characterized by a fall in VVTI and chloride concentration. The successful treatment of heart failure was characterized by a fall in heart rate, an increase in creatinine and sodium concentrations. Dogs receiving diuretics had higher heart rates, lower VVTI, higher urea concentrations, lower potassium, sodium and chloride concentrations. Conclusions: Numerous complex alterations in some of the studied parameters are associated with heart disease, heart failure and their treatment. Further consideration of these changes may improve our skills in diagnosis, prognostication and treatment..
Descriptors: blood composition, creatinine, diagnosis, diuresis, electrocardiography , haematocrit, heart, heart diseases, heart rate, medical treatment, potassium, potassium chloride, sodium, urea.

Chaprazov, T. (2006). **Changes in some clinical and laboratory indices in dogs with experimental Staphylococcus aureus sepsis.** *Bulgarian Journal of Veterinary Medicine* 9(1): 51-60. ISSN: 1311-1477.
Abstract: The study was conducted in 6 clinically healthy dogs that were experimentally infected via intravenous injection of 5 mL broth culture of a field Staphylococcus aureus strain (1.2x109 cells/mL). The dynamics of rectal temperature, heart and respiratory rates and haematological parameters (erythrocyte counts, haematocrit, haemoglobin, erythrocyte sedimentation rate, total and differential leukocyte counts, total protein, fibrinogen, bilirubin, urea, creatinine, pyruvate and lactate) were observed for 28-day period. It was observed that after 2 h of post-infection an increase in body temperature, tachycardia and tachypnea occurred. Followed by a marked leukopenia with an increased leukocyte counts at the 24th h with a left shift were noticed. Statistically significant increased in the values of blood biochemical parameters were observed for fibrinogen and bilirubin, while the concentrations of pyruvate decreased. The levels of total protein, creatinine, urea and lactate remained stable without significant deviations during the entire period of the survey.
Descriptors: bilirubin, blood chemistry, body temperature, clinical aspects, creatinine, disease markers, erythrocytes, experimental infections, fibrinogen, hematocrit, hematology, hemoglobin, heart rate, lactic acid, leukocytes, leukopenia, pathogenesis, pyruvic acid, respiration, septicemia, urea, dogs, *Staphylococcus aureus*.

Chuah, M.K.L., G. Schiedner, L. Thorrez, B. Brown, M. Johnston, V. Gillijns, S. Hertel, N. Van Rooijen, D. Lillicrap, D. Collen, T. Vandendriessche, and S. Kochanek (2003). **Therapeutic factor viii levels and negligible toxicity in mouse and dog models of hemophilia a following gene therapy with high-capacity adenoviral vectors.** *Blood* 101(5): 1734-1743. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: High-capacity adenoviral (HC-Ad) vectors expressing B-domain-deleted human or canine factor VIII from different liver-specific promoters were evaluated for gene therapy of

hemophilia A. Intravenous administration of these vectors into hemophilic FVIII-deficient immunodeficient SCID mice (FVIIIKO-SCID) at a dose of 5X109 infectious units (IU) resulted in efficient hepatic gene delivery and long-term expression of supraphysiologic FVIII levels (exceeding 15 000 mU/mL), correcting the bleeding diathesis. Injection of only 5X107 IU still resulted in therapeutic FVIII levels. In immunocompetent hemophilic FVIII-deficient mice (FVIIIKO), FVIII expression levels peaked at 75 000 mU/mL but declined thereafter because of neutralizing anti-FVIII antibodies and a cellular immune response. Vector administration did not result in thrombocytopenia, anemia, or elevation of the proinflammatory cytokine interleukin-6 (IL-6) and caused no or only transient elevations in serum transaminases. Following transient in vivo depletion of macrophages before gene transfer, significantly higher and stable FVIII expression levels were observed. Injection of only 5X106 HC-Ad vectors after macrophage depletion resulted in long-term therapeutic FVIII levels in the FVIIIKO and FVIIIKO-SCID mice. Intravenous injection of an HC-Ad vector into a hemophilia A dog at a dose of 4.3X109 IU/kg led to transient therapeutic canine FVIII levels that partially corrected whole-blood clotting time. Inhibitory antibodies to canine FVIII could not be detected, and there were no signs of hepatotoxicity or of hematologic abnormalities. These results contribute to a better understanding of the safety and efficacy of HC-Ad vectors and suggest that the therapeutic window of HC-Ad vectors could be improved by minimizing the interaction between HC-Ad vectors and the innate immune system.
Descriptors: blood and lymphatics, transport and circulation, genetics, molecular genetics, biochemistry and molecular biophysics, hemophilia A, blood and lymphatic disease, genetic disease, gene therapy, genetic techniques, laboratory techniques.

Driessen, B., J.S. Jahr, F. Lurie, M.S. Golkaryeh, and R.A. Gunther (2003). **Arterial oxygenation and oxygen delivery after hemoglobin-based oxygen carrier infusion in canine hypovolemic shock: a dose-response study.** *Critical Care Medicine.* 31(6): 1771-9. ISSN: 0090-3493.
Abstract: OBJECTIVE: To compare effects of 6% hetastarch (Hextend) and hemoglobin-based oxygen carrier hemoglobin glutamer-200 (Hb-200) (bovine; Oxyglobin) on hemodynamics, arterial oxygen content, and systemic oxygen delivery in a canine hemorrhagic shock model. DESIGN: Randomized laboratory investigation. SETTING: University surgical research facility. SUBJECTS: Twenty-four anesthetized healthy, adult, mongrel dogs (28 +/- 1 kg; 7 female, 17 male). INTERVENTIONS: Dogs were instrumented for determinations of heart rate, arterial, central venous, pulmonary arterial, and pulmonary arterial occlusion pressures, and cardiac index. Total solids, colloid oncotic pressure, arterial oxygen content, Hb, lactate, pH, and blood gases were analyzed in blood samples. Recordings were made before, after 1 hr of hemorrhagic shock, and immediately and 3 hrs after infusion of either 30 mL/kg hetastarch (group 1), 10 mL/kg Hb-200 + 20 mL/kg hetastarch (group 2), 20 mL/kg Hb-200 + 10 mL/kg hetastarch (group 3), or 30 mL/kg Hb-200 (group 4). MEASUREMENTS AND MAIN RESULTS: Hemorrhage (35 +/- 1 mL/kg) reduced mean arterial pressure to 50 mm Hg and caused significant decreases in total Hb, mean pulmonary arterial pressure, cardiac index and systemic oxygen delivery, increases in heart rate and systemic vascular resistance, and lactic acidosis. In group 1, hetastarch infusion was accompanied by increases of pulmonary arterial pressure, cardiac index, and blood oxygen extraction

above baseline, and decreases of systemic vascular resistance, total Hb, total solids, arterial oxygen content, and systemic oxygen delivery below baseline (p <.05). Other data returned to baseline. In groups 2 to 4, hemodynamic functions (except pulmonary arterial pressure) recovered, yet neither total Hb (i.e., plasma and red blood cell Hb) nor arterial oxygen content increased despite increases in plasma Hb of 2 to 5 g/dL and proportionate increases in total solids. Systemic oxygen delivery improved dose-dependently with Hb-200 but did not return to baseline (p <.05), reaching values comparable to hetastarch group only at 30 mL/kg Hb-200. In all groups, oxygen extraction remained above baseline. Metabolic acidosis and lactatemia resolved significantly faster in groups 2 to 4, and colloid oncotic pressure after resuscitation was greater in groups 2 to 4 than in controls (p <.05). CONCLUSIONS: In hemorrhagic shock, Hb-200 infusion may not improve oxygen delivery more than hetastarch, likely due to hemodilution caused by its high colloid oncotic pressure, but may facilitate diffusive oxygen transport to tissues.
Descriptors: healthy, adult, mongrel dogs, canine hemorrhagic shock model, hemoglobin-based oxygen carrier, hemodynamics, arterial oxygen.

Driessen, B., J.S. Jahr, F. Lurie, and R.A. Gunther (2003). **Effects of resuscitation with hemoglobin glutamer-200 (bovine) on systemic and mesenteric oxygen delivery in a canine hemorrhagic shock model: a comparison with 6 % hetastarch and shed blood.** In: *2003 Annual Meeting of the American Society of Anesthesiologists: Abstracts of Scientific Papers, October 11-15, 2003, San Francisco, CA, USA,* Abstract No. A 398.
Abstract: Introduction: Perfusion and thus O2 supply of the gut diminishes rapidly during hemorrhagic shock, exposing this organ to an increased risk of irreversible hypoxic damage. Hypovolemic resuscitation with Hemoglobin glutamer-200 (Hb-200) has been shown to improve many hemodynamic parameters including mesenteric arterial blood flow (MAF) but failed to restore systemic and mesenteric O2 delivery, while normovolemic shed blood resuscitation did (Driessen et al. Br J Anaesth 2001; 86:683-92). Since hypovolemic shock treatment aimed at restoring O2 transport rather than hemodynamic parameters improves outcome, we studied the efficacy of a larger dose of Hb-200 in comparison with whole blood (WB) and 6 % hetastarch (HES) infusion. Methods: Twelve anesthetized dogs (29 +- 1 kg) were instrumented for recordings of heart rate (HR), mean arterial (MAP) and central venous pressures (CVP), cardiac output, and MAF. Hemoglobin (Hb), O2 content (O2ct), lactate, pH, and blood gases were analyzed in arterial, mixed and mesenteric venous blood samples. Indexes for cardiac output (CI), MAF (MAFI), systemic (sDO2I) and mesenteric O2 delivery (mDO2I), systemic (sO2Ex) and mesenteric O2 extraction ratios (mO2Ex) were calculated. Recordings were made before (baseline), after 1 h of hemorrhage, and immediately and 3 h after resuscitation with 30 mL/kg of either Hb-200, HES, or shed WB. Data analysis included ANOVA plus Dunnett's and Tukey's tests (P < 0.05). Results: Hemorrhage (average 34 +- 2 mL/kg = 40 % blood loss) decreased MAP, CVP, CI, MAFI, sDO2I, mDO2I, total Hb, and arterial O2ct by average 49, 72, 59, 51, 70, 64, 22, and 26 %, respectively and increased HR, sO2Ex and mO2Ex by average 129, 190, and 200 %, respectively (P<0.05). Only WB transfusion restored all hemodynamic, hematological, oxygenation, and acid-base variables at 3 h post treatment. Hb-200 infusion returned most hemodynamic parameters including CI and MAFI to baseline but increased MAP above

baseline (P<0.05). CVP was greater than in the WB group (P<0.05). Hb-200 infusion failed to restore total Hb and arterial O2ct; therefore, sDO2I and mDO2I as well as mixed-venous O2ct and mesenteric venous O2ct remained below baseline (P<0.05). Nevertheless, all systemic and mesenteric acid-base variables recovered after Hb-200 resuscitation. In the HES group, HR and MAFI returned to baseline, but MAP remained below and CI above baseline following resuscitation (P<0.05). HES further decreased total Hb and arterial O2ct, thereby preventing complete recovery of sDO2I and mDO2I (P<0.05). Thus, sO2Ex and mO2Ex stayed above baseline (P<0.05). Also in this group systemic and mesenteric acid-base variables recovered to baseline, yet slower than in the other two groups. Post resuscitation, HES and Hb-200 groups did not differ significantly with respect to total Hb, arterial O2ct, or sDO2I and mDO2I. Still, lactic acidosis resolved faster after Hb-200 than HES infusion (P<0.05). Conclusion: In canine hemorrhagic shock, isovolemic resuscitation with hemoglobin-based oxygen carriers such as Hb-200 may not improve arterial O2ct or systemic and mesenteric O2 delivery more so than HES, but may resolve systemic and mesenteric metabolic acidosis more rapidly than HES due to facilitated O2 transport to tissues. While potentially superior to non-Hb colloids (HES), Hb-200 is not equally effective with WB resuscitation.
Descriptors: pharmacology, respiratory system, respiration, hemorrhagic shock, nervous system disease, vascular disease, mesenteric oxygen delivery, clinical techniques, therapeutic and prophylactic techniques, resuscitation, systemic oxygen delivery, cardiac output, central venous pressure, heart rate, mean arterial pressure, mesenteric arterial blood flow.

Dubin, A., E. Estenssoro, G. Murias, H. Canales, P. Sottile, J. Badie, M. Baran, F. Palizas, M. Laporte, and M. Rivas Diaz (2001). **Effects of hemorrhage on gastrointestinal oxygenation.** *Intensive Care Medicine* 27(12): 1931-1936. ISSN: 0342-4642.
Abstract: OBJECTIVES: (1) To demonstrate that metabolic parameters are better indicators of tissue hypoxia than regional and whole oxygen consumption (VO(2)). (2) To compare intramucosal pH (pHi) in different gastrointestinal segments. DESIGN: Prospective, interventional study. SETTING: Research laboratory at a university center. SUBJECTS: Fourteen anesthetized, mechanically ventilated dogs. INTERVENTIONS: Twenty milliliters per kilogram bleeding. MEASUREMENTS AND MAIN RESULTS: We placed pulmonary, aortic and mesenteric venous catheters, and an electromagnetic flow probe in the superior mesenteric artery, and gastric, jejunal and ileal tonometers to measure flows, arterial and venous blood gases and lactate, and intramucosal PCO(2). We calculated systemic and intestinal oxygen transport (DO(2)) and consumption (VO(2)), pHi and arterial minus intramucosal PCO(2) (DeltaPCO(2)). Then, we bled the dogs and repeated the measurements after 30 min. Systemic and intestinal DO(2) fell (26.0+/-7.3 versus 8.9+/-2.6 and 71.9+/-17.3 versus 24.6+/-9.6 ml/min per kg, respectively, p<0.0001). Systemic and intestinal VO(2) remained unchanged (5.5+/-1.3 versus 5.4+/-1.3 and 15.7+/-5.0 versus 14.9+/-5.3 ml/min per kg, respectively). Gastric, jejunal and ileal pHi (7.13+/-0.11 versus 6.96+/-0.17, 7.18+/-0.06 versus 6.97+/-0.15, 7.12+/-0.11 versus 6.94+/-0.14, p<0.05) and DeltaPCO(2) (21+/-13 versus 35+/-23, 15+/-5 versus 33+/-16, 23+/-17 versus 38+/-20, p<0.05) changed accordingly. Arterial and mesenteric venous lactate and their difference, rose significantly (1.7+/-0.9 versus 3.7+/-1.4 and 1.8+/-0.8 versus 4.3+/-1.5 mmol/l, 0.1+/-0.6 versus 0.6+/-0.7 mmol/l, p<0.05). CONCLUSIONS: During hemorrhage, systemic and intestinal VO(2) remained

stable. However, hyperlactatemia and intramucosal acidosis evidenced anaerobic metabolism. pHi changes paralleled in the three intestinal segments.
Descriptors: animal model, tissue hypoxia, hemorrhage, pH changes, gastrointestinal segments.

Friedman, Z., H. Berkenstadt, S. Preisman, and A. Perel (2003). **A comparison of lactated ringer's solution to hydroxyethyl starch 6% in a model of severe hemorrhagic shock and continuous bleeding in dogs.** *Anesthesia and Analgesia* 96(1): 39-45. ISSN: 0003-2999.
Abstract: In this randomized, controlled study in dogs, we examined the short-term effects of blood pressure targeted fluid resuscitation with colloids or crystalloids solutions on systemic oxygen delivery, and lactate blood concentration. Fluid resuscitation using hydroxyethyl starch (HES) 6% to a mean arterial blood pressure (MAP) of 60 mm Hg was compared with lactated Ringer's solution (LR) to a MAP of 60 or 80 mm Hg (LR60 and LR80, respectively). The model was one of withdrawal of blood to a MAP of 40 mm Hg through an arterial catheter that was then connected to a system allowing bleeding to occur throughout the study whenever MAP exceeded 40 mm Hg. Target MAP was maintained for 60 min with a continuous infusion of the designated fluid replacement. All 15 dogs (5 in each group) survived until the last measurement. Blood loss in the LR80 group (2980+-503 mL) (all values mean+-SD) was larger than in the LR60 and HES60 groups (1800+-389 mL, and 1820+-219 mL, respectively) (P<0.001). Whereas 840+-219 mL of HES60 was needed to maintain target MAP, 1880+-425 mL of LR was needed in the LR60 group, and 4590+-930 mL in the LR80 group (P<0.001). Lactate blood concentrations were smaller and delivered O2 higher in the HES60 group (35+-17 mg/dL and 239+-61 mL/min, respectively) in comparison to the LR60 group (89+-18 mg/dL and 140+-48 mL/min, respectively) and the LR80 group (75+-23 mg/dL and 153+-17 mL/min, respectively) (P=0.02 and P=0.026). In conclusion, fluid resuscitation during uncontrolled bleeding, to a target MAP of 60 mm Hg, using HES60 resulted in larger oxygen delivery and smaller systemic lactate A resuscitation to a target MAP of 60 or 80 mm Hg using LR.
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, miscellaneous substances, hemorrhagic shock, vascular disease, therapy, fluid resuscitation, clinical techniques, therapeutic and prophylactic techniques, continuously bleeding, lactated ringer's solution, mean arterial blood pressure, six percent hydroxyethyl starch solution.

Gargiulo, N.J.3., F.J. Veith, T. Ohki, L.A. Scher, G.L. Berdejo, E.C. Lipsitz, M. Menegus, and M. Greenberg (2007). **Histologic and duplex comparison of the perclose and angio-seal percutaneous closure devices.** *Vascular* 15(1): 24-9. ISSN: 1708-5381.
Abstract: The intravascular and extravascular effects of percutaneous closure devices have not been well studied. We assessed the performance and healing characteristics in dogs of two devices approved by the US Food and Drug Administration. Nine adult male dogs were anesthesized prior to percutaneous access of both femoral arteries with a 6F sheath. All dogs were systemically heparinized to an activated clotting time (ACT) > 250 seconds. Duplex sonography was performed preoperatively to measure vessel diameter and flow velocity. In each dog, one of two devices (Perclose, Abbot Laboratories, Abbott Park, IL or Angio-Seal, St. Jude Medical, St. Paul, MN) was randomly deployed into one of the two femoral arteries.

The other device was deployed on the opposite side. Duplex sonography was repeated immediately after deployment and 28 days later to measure changes in vessel diameter and flow velocity. At 28 days, angiography was performed on both femoral arteries before they were removed for histologic evaluation. The time required to excise each vessel reflected the degree of scarring. Hemostasis time for the Angio-Seal device far surpassed the Perclose device (39 +/- 7 vs 0 minutes; $p < .05$). Vessel narrowing was observed only at 28 days after deployment of the Angio-Seal device ($p < .05$). Extensive extravascular scarring was observed with the Angio-Seal device, which resulted in a longer femoral artery dissection time and greater periadventitial scar thickness compared with the Perclose device ($p < .05$). When compared with the Perclose suture closure device, the Angio-Seal collagen plug closure device prolonged hemostasis time and produced greater vessel narrowing and periadventitial inflammation (extravascular scarring) in a canine model at 4 weeks.

Descriptors: femoral artery surgery, hemostasis, surgical instrumentation, cicatrix pathology, dogs, femoral artery pathology, femoral artery ultrasonography, hemostasis, surgical methods, hyperplasia pathology, models, animal, time factors, ultrasonography, doppler, duplex methods, wound healing physiology.

Gunther, R., B. Driessen, F. Lurie, and J. Jahr (2003). **Plasma hemoglobin contribution to oxygen consumption by a hemoglobin-based oxygen carriers in a canine hypovolemia model.** *FASEB Journal* 17(4-5): Abstract No. 806.4. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, hypovolemia, blood and lymphatic disease, splenectomy, experimental surgical techniques, laboratory techniques, arterial partial oxygen pressure, venous partial oxygen pressure, arterial oxygen content, oxygen consumption, oxygen delivery, oxygen saturation, venous oxygen content.

Harding, T.C., K.E. Koprivnikar, G.H. Tu, N. Zayek, S. Lew, A. Subramanian, A. Sivakumaran, D. Frey, K. Ho, M.J. Vanroey, T.C. Nichols, D.A. Bellinger, S. Yendluri, J. Waugh, J. Mcarthur, G. Veres, and B.A. Donahue (2004). **Intravenous administration of an aav-2 vector for the expression of factor ix in mice and a dog model of hemophilia b.** *Gene Therapy* 11(2): 204-213. ISSN: 0969-7128.

Abstract: Previous experiments have demonstrated the stable expression of factor IX (FIX) protein in mice and canine models of hemophilia B following portal vein gene transfer with a recombinant adeno-associated virus (rAAV) vector encoding FIX. Here, we present the results of studies that further optimized the rAAV vector transgene cassette used to express FIX and explored the use of the less-invasive intravenous (i.v.) route of vector administration for the treatment of hemophilia B. First, a liver-specific promoter was evaluated in conjunction with cis-acting regulatory elements in mice. Constructs that included both the beta-globin intron and the woodchuck hepatitis virus post-transcriptional regulatory element resulted in the highest level of FIX expression in vivo. Using this optimized vector, we demonstrate that i.v. injection was feasible for hepatic gene transfer in mice, achieving 70-80% of portal vein expression levels of FIX. In further studies using the Chapel Hill strain of hemophilia B dogs, we demonstrate for the first time FIX expression and partial correction of the bleeding disorder following i.v. administration of an AAV vector.

Descriptors: blood and lymphatics, transport and circulation, cell biology, methods and techniques, molecular genetics, biochemistry and molecular biophysics, hemophilia B, blood and lymphatic disease, genetic disease, genetics, therapy, hepatic gene transfer, clinical techniques, intravenous vector administration, genetic techniques, portal vein gene transfer, clinical techniques, genetic techniques, laboratory techniques, therapeutic and prophylactic techniques.

Hayashi, K. (2003). **Effects of angiotensin ii receptor antagonist on intestinal mucosal oxygenation during canine isovolemic hemodilution with hydroxyethyl starch.** *Japanese Journal of Anesthesiology* 52(6): 603-610. ISSN: 0021-4892.
Abstract: Background: Although isovolemic hemodilution can be used clinically to reduce the need for blood transfusion, the critical hemoglobin level and severe indequacy of tissue oxygenation induced by hemodilution remain unknown. Methods: Anesthetized dogs were submitted to graded hemodilution (20% and 40% blood volume reductions of estimated circulating blood volume) replaced with 10% hydroxyethyl starch. The effect of angiotensin II receptor (AT-II) antagonist, candesartan, on the intestinal mucosal oxygenation was assessed by tonometric method. Results: The splanchnic blood flow, measured by transit-time flow meters, and intestinal mucosal oxygenation were maintained well during 20% blood volume reduction without AT-II antagonist. By severe blood volume reduction, however, inadequate oxygenation was observed without, but not with AT-II antagonist. Conclusions: These results suggest the protective effect of AT-II antagonist on intestinal perfusion during severe isovolemic hemodilution. Further investigation will be needed in patients undergoing major surgery with large anticipated blood loss.
Descriptors: blood and lymphatics, transport and circulation, pharmacology, isovolemic hemodilution, clinical techniques, therapeutic and prophylactic techniques.
Language of Text: Japanese.

Horwitz, M., K.F. Benson, Z. Duan, F.Q. Li, and R.E. Person (2004). **Hereditary neutropenia: dogs explain human neutrophil elastase mutations**. *Trends in Molecular Medicine* 10(4): 163-170 ISSN: 1471-4914.
NAL Call Number: QH506
Abstract: Mutations in ELA2 the gene encoding neutrophil elastase (NE), cause the human diseases cyclic neutropenia (CN) and severe congenital neutropenia (SCN). Numerous mutations are known, but their lack of consistent biochemical effect has proven puzzling. The recent finding that mutation of AP3B1, which encodes the P subunit of adaptor protein complex 3 (AP3), is the cause of canine CN suggests a model for the molecular basis of hereditary neutropenias, involving the mistrafficking of NE: AP3 recognizes NE as a cargo protein, and their interaction implies that NE is a transmembrane protein. Computerized algorithms predict two NE transmembrane domains. Most CN mutations fall within predicted transmembrane domains and lead to excessive deposition of NE in granules, whereas SCN mutations usually disrupt the AP3 recognition sequence, resulting in excessive transport to the plasma membrane.
Descriptors: molecular genetics, biochemistry and molecular biophysics, cyclic neutropenia, blood and lymphatic disease, genetics, hereditary neutropenia, blood and lymphatic disease,

genetic disease, immune system disease, severe congenital neutropenia, computerized algorithm, mathematical and computer techniques, gene product interactions.

Jensen, T.B., O. Rahbek, S. Overgaard, and K. Soballe (2004). **Platelet rich plasma and fresh frozen bone allograft as enhancement of implant fixation - an experimental study in dogs**. *Journal of Orthopaedic Research* 22(3): 653-658. ISSN: 0736-0266.
Descriptors: blood and lymphatics, transport and circulation, skeletal system, movement and support, surgery, medical sciences, bone grafting, clinical techniques, therapeutic and prophylactic techniques, implant fixation, clinical techniques, titanium alloy implant, prosthetic, bone formation, enhancement, gap healing, enhancement.

Koide, M., S. Nishizawa, M. Yamaguchi, Y. Nonaka, and H. Namba (2004). **Chronological changes of diameter, functional properties, and morphology of vasospastic artery in canine two-hemorrhage model.** *Journal of Pharmacological Sciences* 94(Supplement 1): 94P. ISSN: 1347-8613.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, models and simulations, computational biology, hemorrhage, vascular disease, chronological changes, two hemorrhage model.

Lavergne, S.N. and L.A. Trepanier (2007). **Anti-platelet antibodies in a natural animal model of sulphonamide-associated thrombocytopaenia.** *Platelets* 18(8): 595-604. ISSN: 0953-7104.
Abstract: Delayed hypersensitivity (HS) reactions to sulphonamide antimicrobials occur in both humans and dogs with a similar clinical presentation, and may include thrombocytopaenia. Drug-dependent anti-platelet antibodies have been identified in humans with sulphonamide-associated thrombocytopaenia. Our purpose was to determine whether similar antibodies were present in dogs with sulphonamide-associated thrombocytopaenia. Flow cytometry was used to detect anti-platelet antibodies in sera from 32 dogs with sulphonamide HS, eight dogs that tolerated sulphonamide therapy without adverse reactions and nine healthy control dogs were used as controls. Anti-platelet antibodies were found more frequently, with significantly stronger fluorescence signals, in HS dogs (75%) compared to 'tolerant' dogs (38%), and in HS dogs with thrombocytopaenia (90%) compared to HS dogs with normal platelet counts (46%). Binding to platelets was enhanced in the presence of soluble sulphonamide in 42% of positive samples. Experiments with canine Glanzmann's platelets, and competition assays with fibrinogen fragments or anti-GP antibodies, did not support the hypothesis that these canine antibodies target the fibrinogen receptor. In conclusion, anti-platelet antibodies were identified in dogs with sulphonamide-associated thrombocytopaenia, which suggests a similar immunopathogenesis for this reaction in dogs as seen in humans. Further work in both species will determine whether these antibodies are pathogenic in vitro.
Descriptors: autoantibodies blood, blood platelets immunology, drug hypersensitivity, sulfonamides adverse effects, thrombocytopenia chemically induced, dogs, flow cytometry, models, animal, thrombocytopenia immunology.

Lee, R.S., C.S. Kuhr, G.E. Sale, E. Zellmer, W.J. Hogan, R. Storb, and M.T. Little (2003). **Fty720 does not abrogate acute graft-versus-host disease in the dog leukocyte antigen-nonidentical unrelated canine model.** *Transplantation* 76(8): 1155-1158. ISSN: 0041-1337.
NAL Call Number: QP89.T73
Abstract: Background. Acute graft-versus-host disease (GVHD) remains a significant impediment to successful hematopoietic stem-cell transplantation (HSCT). Here, we examined the effectiveness of 2-amino-2-(2-(4-octylphenyl)ethyl)-1,3-propanediol hydrochloride (FTY720), an immunosuppressant that retraffics activated lymphocytes to secondary lymphoid organs, for the treatment of acute GVHD in an established dog leukocyte antigen-nonidentical unrelated canine HSCT model. Methods. Dogs were given HSCT after conditioning with 920 cGy total body irradiation. The dogs received methotrexate 0.4 mg/kg/day on days 1, 3, 6, and 11 and FTY720 (5 mg/kg/day orally) after developing GVHD. Results. Five of six dogs achieved engraftment, developed acute GVHD, and were treated with FTY720. FTY720 resulted in a profound decrease in lymphocytes and a temporary mitigation of clinical GVHD; however, GVHD recurred in all dogs. Four of five dogs were euthanized because of severe GVHD and the fifth because of severe inanition associated with moderate GVHD. Conclusions. Compared with controls, treatment of GVHD with FTY720 did not control this complication or significantly increase survival.
Descriptors: blood and lymphatics, transport and circulation, methods and techniques, pharmacology, acute graft vs host disease, immune system disease, hematopoietic stem cell transplantation, laboratory techniques, dog leukocyte antigen nonidentical unrelated donor, engraftment.

Lesnikova, M., M.C. Jensen, A. Bukovsky, A. Nikitine, B. Thomasson, J. Morris, R.F. Storb, H.P. Kiem, R.A. Nash, and G.E. Georges (2003). **Resistance to mycophenolate mofetil (mmf) after lentiviral transduction of canine t cells with a mutant impdh vector.** *Blood* 102(11): 499B. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Several clinical studies of adoptive immunotherapy with genetically modified (GM) donor T cells infused after allogeneic hematopoietic cell transplantation (HCT) have shown limited in vivo function of the ex vivo expanded T cells. Multiple factors including duration of ex vivo cell culture, immunogenicity of the transgene, lack of a selective advantage for the GM T cells and insufficient preclinical data in large animal models may have impaired successful clinical translation of this approach. To help address these problems, we constructed a self-inactivating, replication incompetent lentiviral vector expressing a (Thr-333fwdarwIle, Ser-351fwdarwTyr) trans-dominant mutant inosine monophosphate dehydrogenase II (IMPDH*), which renders transduced T cells resistant to MMF with intact de novo guanosine synthesis. MMF administration after infusion of IMPDH* transduced T cells would inhibit host immune responses to the GM T cells and provide a proliferative advantage for transduced T cells. Lentiviral vector transduction can reduce the time in culture since T cell proliferation is not required. In preparation for in vivo studies in the dog model of allogeneic HCT, we first confirmed function of the IMPDH* vector in immortalized T cell lines and then optimized conditions for lentiviral transduciton of fresh, primary dog T cells to achieve 20-30% transduction efficiency. Replication incompetent, VSV-G pseudotyped IMPDH* lentiviral vector, pRRLsin.cPPT.MSCV.IMPDH*.Wpre, was pre-

pared from transiently transfected 293T cells. Immortalized dog T lymphocyte CLGL-90 cells were transduced with IMPDH* lentiviral vector and selected in 1 muM MMF for 14 days. Transduced cells were cloned by limiting dilution and assayed for MMF resistance. All IMPDH* CLGL-90 clones were uniformly resistant to MMF 0.1 to 10 muM, compared to control CLGL cells. Quantitative TaqMan PCR assay with lentiviral-specific primers showed transduced CLGL clones had up to 3 lentiviral vector insertion copies per clone. Next, fresh CD3+ T cells were isolated from dog peripheral blood with immunomagnetic selection (Miltenyi) or plastic adherence to >90% purity. Cells were cultured with IL-2 (10 IU/mL) and IL-7 (20 ng/mL) for 72 hours. T cells were transduced once at an MOI of 20 with the spinoculation method. Transduced cells were stimulated after 24 hours with MHC-mismatched dendritic cells (DC) (10:1 responder: stimulator ratio) and selected in 0.5 muM MMF 2 days later. After 2nd stimulation with DCs, cells were assessed for proliferation with 3H-thymidine uptake. In the presence of MMF, IMPDH* transduced cells had 3-fold increased proliferation over nontransduced control T cells. In summary, lentiviral vector expressing trans-dominant mutant IMPDH* rendered transduced dog T cells resistant to MMF. These results establish the IMPDH* vector as a tool to confer in vivo resistance to MMF. We are planning adoptive immunotherapy studies with infusion of IMPDH* transduced donor T cells into recipient dogs treated with MMF after allogeneic HCT to determine the feasibility of in vivo selection of GM T cells.

Descriptors: blood and lymphatics, transport and circulation, immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, pharmacology, adoptive immunotherapy, clinical techniques, immunologic techniques, laboratory techniques, therapeutic and prophylactic techniques, allogeneic hematopoietic cell transplantation, clinical techniques, lentivirus transduction, drug resistance mechanism, host immune response, transduction efficiency.

Letsou, G.V., E.M. Breznock, J. Whitehair, R.S. Kurtz, R. Jacobs, M.L. Leavitt, H. Sternberg, S. Shermer, S. Kehrer, J.M. Segall, M.A. Voelker, H.D. Waitz, and P.E. Segall (2003). **Resuscitating hypothermic dogs after 2 hours of circulatory arrest below 6degreec.** *Journal of Trauma Injury Infection and Critical Care* 54(5 Supplement): S177-S182. ISSN: 1079-6061.

Abstract: Background: Ultraprofound hypothermia may have a place in trauma rescue and resuscitation. We describe resuscitation of dogs after asanguineous perfusion and circulatory arrest of 2 hours at 2degree to 4degreeC. Methods: Nine dogs were cooled using a bypass apparatus and their circulating blood replaced with bicarbonated Hextend (Abbott, North Chicago, IL). Perfusion was continued to 2degree to 4degreeC, and 60 mL of 2 mol/L KCl and 20 mL of 50% MgSO4cntdot7H2O were infused intra-arterially, and circulation was arrested for 2 hours. The dogs were then rewarmed, transfused, defibrillated, weaned from by-pass, and allowed to awaken. Preoperative and postoperative biochemistry and hematology were compared. Results: Six dogs recovered fully. One of these dogs died of an infection 2 weeks later. Three other dogs never recovered because of technical or procedural difficulties. Biochemical and hematologic parameters were normal by 3 weeks. Conclusion: Hypothermic blood substitution with Hextend allows resuscitation after 2 hours of ice-cold circulatory arrest in dogs.

Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, methods and techniques, circu-

latory arrest, vascular disease, resuscitation, clinical techniques, therapeutic and prophylactic techniques, hypothermia.

Lurie, F., B. Driessen, J.S. Jahr, R. Reynoso, and R.A. Gunther (2003). **Validity of arterial and mixed venous oxygen saturation measurements in a canine hemorrhage model after resuscitation with varying concentrations of hemoglobin-based oxygen carrier.** *Anesthesia and Analgesia* 96(1): 46-50. ISSN: 0003-2999.

Abstract: In this study, we evaluated the validity of saturation measurements in mixed venous and arterial blood during posthemorrhagic anemia and resuscitation with varying levels of hemoglobin-based oxygen carrier (Hemoglobin glutamer-200 (bovine); Oxyglobin(R) (Hb-200)). Nineteen anesthetized, splenectomized, mixed-breed dogs were anesthetized (two were excluded from the data because they did not survive the exsanguination, supporting the validity of the model). Their pulmonary arteries were cannulated with the Abbott QVUE Oximetrix 3 catheter. An 18-gauge catheter was placed in the femoral artery, and a reusable Nellcor probe was applied to the tongue. Mixed venous and arterial samples were drawn at baseline, after 40% hemorrhage (to keep arterial pressure at 50 mm Hg), and postresuscitation with 30 mL/kg of 6% hetastarch in lactated Ringer's solution (n=4), 10 mL/kg of Hb-200, 20 mL/kg of hetastarch (n=6), 20 mL/kg of Hb-200, and 10 mL/kg of hetastarch (n=7). Samples were compared with oxygen content from the LEXO2CON-K oxygen analyzer, and oxygen content was calculated for all values from the monitors. Results were compared by using analysis of variance. There was good correlation (0.97gtoreqrgtoreq0.92) for the measured versus calculated hemoglobin oxygen saturation values at baseline. After resuscitation, the correlation between calculated and measured values of oxygen content was significantly smaller for all tested instruments. The values of oxygen content calculated from the oxygen saturation monitor and from the oximetric pulmonary artery can deviate by as much as 20% from directly measured values. We conclude that the administration of this oxygen therapeutic may interfere with the values of some monitors.

Descriptors: blood and lymphatics, transport and circulation, pharmacology, posthemorrhagic anemia, blood and lymphatic disease, resuscitation, clinical techniques, therapeutic and prophylactic techniques, oxygen saturation, arterial, mixed venous, validity .

Lurie, F., J.S. Jahr, B. Driessen, V. Bezdikian, and R.A. Gunther (2003). **Measuring circulating blood volume using infused hemoglobin-based oxygen carrier (hboc, oxyglobin(r)) as an indicator: validation in a canine hypovolemia model.** *2003 Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, USA; October 11-15, 2003, Abstract No. A 729.*

Abstract: Direct determination of the circulating blood volume (CBV) is clinically desirable, especially when hemodynamic parameters such as blood pressure and heart rate are pharmacologically altered and may not be used with confidence for monitoring of CBV. In a rabbit model, we demonstrated that small volumes of HBOC may be used for measuring of CBV using the indicator-dilution technique (1). This study was aimed to validate this technique in a canine hypovolemia model with varying concentrations of infused HBOC. Methods: Twenty-four healthy mongrel dogs were anesthetized and anesthesia maintained with isoflurane in 21% oxygen and sufentanil infusion. All animals were mechanically ventilated. After splenectomy and insertion of arterial, venous, and balloon-tipped pulmonary arterial

catheters, and recording of baseline values of total (HbTot) and plasma hemoglobin (HbPla), hematocrit (Hct), and major hemodynamic parameters, dogs were bled (average 36.6 +- 5.8 mL/kg) to a mean arterial pressure of 50 mmHg and maintained hypovolemic for 1 h. Thereafter, measurements were repeated and dogs were resuscitated. Animals in Group 1 were resuscitated with 30 mL/kg of 6 % hetastarch solution (HES; Hextend(R), Abbott, Chicago, Il). Animals in other groups received either 10 mL/kg of hemoglobin glutamer-200 (Hb-200; Oxyglobin(R), Biopure, Cambridge, MA) plus 20 mL/kg HES (Group 2), 20 mL/kg Hb-200 plus 10 mL/kg HES (Group 3), or 30 mL/kg Hb-200 (Group 4). Solutions were infused at 30 mL/kg/h. Measurements were repeated immediately after volume resuscitation. Plasma Hb (HbPla) concentration was determined after centrifugation using the HemoCue(R) (Angelholm, Sweden). Lactated Ringer's solution was infused in all subjects at 5mL/kg/hour for maintenance. CBV at baseline was estimated as 85 mL/kg. CBV values immediately post hemorrhage were calculated by subtracting the volume of withdrawn blood from the baseline value. Based on the assumption that hemorrhage and subsequent volume resuscitation would not cause any hemolysis (as confirmed in group 1), all HbPla was considered to represent infused HBOC. The calculation of CBV using HBOC as an indicator was performed as previously published (1). CBV values derived from measured HBOC concentrations in plasma were compared to calculated (based on an original CBV of 85 mL/kg and withdrawn blood volume) values of CBV utilizing the Bland-Altman analysis, and by linear correlation. Agreement between the methods was analyzed by calculating the bias estimated by the mean difference and the standard deviation of the difference. Results: Calculated and measured CBV values were highly correlated (r=0.97). The difference between indicator dilution-derived and calculated values of CBV did not exceed 4% of calculated CBV in 97% of the measurements. The mean difference between measured and calculated values of CBV was 72 +/- 16 mL, and did not vary significantly between groups 2, 3, and 4 (at varying concentrations of HBOC infused). Conclusions: In a canine hypovolemia model, knowing both the HBOC volume infused and the HBOC concentration measured in plasma allows for reliably determining the circulating blood volume. Our data validate the indicator-dilution technique with HBOC as an appropriate and clinically valuable method for monitoring CBV in treatment of hypovolemia..

Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, pharmacology, hemorrhage, vascular disease, drug therapy, bland altman analysis, mathematical and computer techniques, centrifugation, laboratory techniques, linear correlation, mathematical and computer techniques, blood pressure, heart rate, hematocrit, hemodynamic parameters, hemolysis, hypovolemia, mean circulating blood volume.

Maalaej, N. and J.D. Folts (1996). **Increased shear stress overcomes the antithrombotic platelet inhibitory effect of aspirin in stenosed dog coronary arteries**. *Circulation* 93(6): 1201-1205. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8

Abstract: Background: Shear stress is one of the known platelet activating mechanisms that leads to thrombosis. Increased shear stress has also been postulated to reverse the antithrombotic effect of some drugs such as aspirin (ASA). Methods and Results: Experiments were conducted in five dogs to determine the minimal shear stress levels that produce acute plate-

let thrombus formation in mechanically stenosed arteries and the increase in shear required to reverse the antithrombotic effect of ASA. After intimal and medial damage, stenosis was produced in the circumflex coronary artery. We used the finite-difference numerical solution of the Navier-Stokes equation to determine the wall shear stresses in the area of stenosis. At 70 +- 6% coronary diameter reduction, cyclic flow reductions (CFRs) caused by acute platelet thrombus formation were observed in the stenosed lumen. At this level of stenosis, the shear stress was 144 +- 15 Pa. ASA given at a dose of 5 mg/kg IV inhibited in vivo acute platelet-mediated thrombus formation and abolished CFRs in all dogs. However, increasing the stenosis level to 80 +- 5% caused the CFRs to return. The shear stress increased with the increased level of stenosis to 226 +- 22 Pa. Thus, an average 10% increase in diameter narrowing caused a 56 +- 20% increase in shear stress (P lt .005) and renewed platelet activation and thrombus formation despite ASA pretreatment. Conclusions: Individuals who take ASA daily to prevent coronary artery thrombus formation may not be well protected when a change in hemodynamics, such as an acute hypertensive episode, or an increase in stenosis severity due to a ruptured atherosclerotic plaque causes an increase in shear stress.
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, pharmacology, anticoagulant drug, aspirin, thrombosis.

Miao, C.H., H. Jiang, and B. Sun (1997). **Inhaled nitric oxide improves ventilation efficiency and hemodynamic properties in dogs with endotoxin induced acute respiratory distress syndrome**. *Pediatric Research* 41(4 PART 2): 36A ISSN: 0031-3998.
NAL Call Number: RJ1.P4
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, toxicology, cardiovascular drug, critical care, endotoxin induced acute respiratory distress syndrome, gas exchange, hemodynamic properties, inhaled administration efficacy, nitric oxide, pharmacodynamics, pharmacokinetics, pharmacology, respiratory system, respiratory system disease, ventilation efficiency.

Mink, S.N., H. Jacobs, K. Duke, D. Bose, Z.Q. Cheng, and R.B. Light (2004). **N,N',N"-triacetylglucosamine, an inhibitor of lysozyme, prevents myocardial depression in Escherichia coli sepsis in dogs.** *Critical Care Medicine.* 32(1): 184-93. ISSN: 0090-3493.
Abstract: OBJECTIVE: Reversible myocardial depression in sepsis has been ascribed to the release of inflammatory mediators. We recently found that lysozyme c (Lzm-S), consistent with that originating from the spleen, was a mediator of myocardial depression in an Escherichia coli model of septic shock in dogs. We further showed in a right ventricular trabecular (RVT) preparation that Lzm-S's depressant activity could be blocked by N,N',N" triacetylglucosamine (TAC), a competitive inhibitor of Lzm-S. We hypothesized that Lzm-S binds to or cleaves a cardiac membrane glycoprotein, thereby interfering with myocardial contraction in sepsis. In the present study, we examined whether TAC could prevent myocardial depression in an in vivo preparation and whether other related N-acetylglucosamine (NAG) structures could also inhibit Lzm-S's effect in RVT. DESIGN: Randomized experimental study. SETTING: University laboratory. SUBJECTS: Anesthetized, mechanically ventilated dogs. INTERVENTIONS: We produced sepsis by infusion of E. coli over an approximately 6-hr period. MEASUREMENTS AND MAIN RESULTS: We examined the effect of TAC

on stroke work, our primary index of myocardial function, when treatment was administered before sepsis (pretreatment) and after 1.5 hrs (early treatment study) and 3.5 hrs of sepsis (late treatment study; LTS). In the pretreatment study and early treatment study, myocardial depression would have not yet occurred but would have already been present in the late treatment study. In RVT, we assessed the effect of other NAG oligosaccharides and variants to the NAG structure on Lzm-S's depressant activity. In pretreatment and the early treatment study, TAC prevented the reduction in stroke work observed in nontreated septic groups but did not reverse the reduction found in the late treatment study. In RVT, of the compounds tested, only N,N'-diacetylglucosamine showed an inhibitory effect. CONCLUSIONS: We found that TAC, a competitive inhibitor of Lzm-S, prevented myocardial depression in experimental sepsis. Only specific NAG structures are inhibitory to Lzm-S's depressant activity. TAC may be useful in attenuating cardiovascular collapse in sepsis.
Descriptors: animal model, Escherichia coli, sepsis, septic shock model, anesthetized, mechanically ventilated, sepsis, cardiovascular collapse.

Minneci, P.C., K.J. Deans, S. Shiva, H. Zhi, S.M. Banks, S. Kern, C. Natanson, S.B. Solomon, and M.T. Gladwin (2008). **Nitrite reductase activity of hemoglobin as a systemic nitric oxide generator mechanism to detoxify plasma hemoglobin produced during hemolysis.** *American Journal of Physiology. Heart and Circulatory Physiology* 295(2): H743-54. ISSN: 0363-6135.
NAL Call Number: 447.8 Am3
Abstract: Hemoglobin (Hb) potently inactivates the nitric oxide (NO) radical via a dioxygenation reaction forming nitrate (NO(3)(-)). This inactivation produces endothelial dysfunction during hemolytic conditions and may contribute to the vascular complications of Hb-based blood substitutes. Hb also functions as a nitrite (NO(2)(-)) reductase, converting nitrite into NO as it deoxygenates. We hypothesized that during intravascular hemolysis, nitrite infusions would limit the vasoconstrictive properties of plasma Hb. In a canine model of low- and high-intensity hypotonic intravascular hemolysis, we characterized hemodynamic responses to nitrite infusions. Hemolysis increased systemic and pulmonary arterial pressures and systemic vascular resistance. Hemolysis also inhibited NO-dependent pulmonary and systemic vasodilation by the NO donor sodium nitroprusside. Compared with nitroprusside, nitrite demonstrated unique effects by not only inhibiting hemolysis-associated vasoconstriction but also by potentiating vasodilation at plasma Hb concentrations of <25 muM. We also observed an interaction between plasma Hb levels and nitrite to augment nitroprusside-induced vasodilation of the pulmonary and systemic circulation. This nitrite reductase activity of Hb in vivo was recapitulated in vitro using a mitochondrial NO sensor system. Nitrite infusions may promote NO generation from Hb while maintaining oxygen delivery; this effect could be harnessed to treat hemolytic conditions and to detoxify Hb-based blood substitutes.
Descriptors: blood substitutes toxicity, hemodynamics drug effects, hemoglobins metabolism, hemolysis drug effects, nitric oxide metabolism, nitrite reductases blood, sodium nitrite pharmacology, vasodilator agents pharmacology, biosensing techniques, blood pressure drug effects, dogs, dose response relationship, drug, infusions, intravenous, mitochondria, liver drug effects, mitochondria, liver enzymology, models, animal, nitroprusside pharmacology, rats, rats, sprague dawley, sodium nitrite administration and dosage, sodium nitrite phar-

macokinetics, time factors, vascular resistance drug effects, vasoconstriction drug effects, vasodilation drug effects, vasodilator agents administration and dosage, vasodilator agents pharmacokinetics.

Mitaka, C., Y. Hirata, K. Yokoyama, K. Makita, and T. Imai (2001). **A selective inhibitor for inducible nitric oxide synthase improves hypotension and lactic acidosis in canine endotoxic shock.** *Critical Care Medicine.* 29(11): 2156-61. ISSN: 0090-3493.
Abstract: OBJECTIVE: To investigate whether ONO-1714, a putative selective inhibitor for inducible nitric oxide synthase, modulates systemic hemodynamics, arterial blood gases, lactate concentrations, gastric mucosal perfusion, and renal and hepatic functions in endotoxic shock. DESIGN: Prospective, randomized, controlled animal study. SETTING: Laboratory at a university hospital. SUBJECTS: Eighteen male beagle dogs (12-19 kg) under pentobarbital anesthesia. INTERVENTIONS: Dogs were mechanically ventilated and monitored with a pulmonary arterial catheter and a gastric tonometer. They were divided in three groups: a) lipopolysaccharide (LPS) plus vehicle group (n = 6), which received LPS (250 ng/kg/min for 2 hrs) and saline 1 hr later; b) LPS plus ONO (0.05) group (n = 6), which received ONO-1714 (0.05 mg/kg) 1 hr after the start of LPS; c) LPS plus ONO (0.1) group (n = 6), which received ONO-1714 (0.1 mg/kg) 1 hr after the start of LPS. MEASUREMENTS AND MAIN RESULTS: Hemodynamics, blood gas parameters, gastric intramural pH, urine output, and serum levels of lactate, transaminases, bilirubin, and creatinine were measured during a 6-hr observation period. LPS induced hypotension, lactic acidosis, gastric mucosal acidosis, and renal and hepatic dysfunction. ONO-1714 reversed the LPS-induced hypotension and lactic acidosis without deteriorating cardiac output, oxygen delivery, or gastric mucosal acidosis. CONCLUSIONS: These findings suggest that ONO-1714 is a useful agent to reverse hypotension and lactic acidosis in a canine endotoxic shock model.
Descriptors: animal model, endotoxic shock, ONO-1714, selective inhibitor, nitric oxide synthase, hemodynamics.

Obra, R., E.J. Harper, and J. Lunec (1999). **Exercise in healthy adult dogs increases plasma tbars-an indicator of oxidative stress**. *FASEB Journal* 13(4 Part 1): A565. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: biochemistry and molecular biophysics, physiology, hplc, high performance liquid chromatography, measurement method, exercise, oxidative stress, exercise induced, meeting abstract.

Ovlisen, K., A.T. Kristensen, and M. Tranholm (2008). **In vivo models of haemophilia - status on current knowledge of clinical phenotypes and therapeutic interventions.** *Haemophilia the Official Journal of the World Federation of Hemophilia* 14(2): 248-59.
Abstract: Animal models have contributed immensely to the understanding of and the improvement in treatment of haemophilia A and B. First, establishment of haemophilic dog colonies provided an invaluable opportunity to investigate the diseases and later, the advances in gene technologies resulting in small haemophilic animal models were a milestone in the preclinical research making it possible to address some of the many unanswered questions. This review provides an overview of animal models used in the study of haemophilia as well as a short overview of the contributions resulting from studies in these models.

Descriptors: hemophilia a drug therapy, hemophilia a genetics, models, animal, breeding, disease models, animal, dogs, genetic engineering, hemostatics therapeutic use, mice, mice, transgenic, rabbits.

Raife, T., K.D. Friedman, and B. Fenwick (2004). **Lepirudin prevents lethal effects of shiga toxin in a canine model**. *Thrombosis and Haemostasis* 92(2): 387-393. ISSN: 0340-6245.
Abstract: Microvascular thrombosis is a major cause of organ damage in Shiga toxin-mediated hemolytic uremic syndrome (Stx-HUS). In vitro and clinical studies implicate thrombin-mediated mechanisms in the pathogenesis of Stx microvascular thrombosis. In a greyhound model, administration of 0.03 mug/kg to 0.05mug/kg Stx1 or Stx2 causes severe bloody diarrhea and HUS with microvascular thrombosis requiring humane euthanasia within 65 hours. Using a greyhound model of Stx-HUS we analyzed early hemostatic changes, and tested the hypothesis that thrombin blockade with lepirudin would prevent lethal Stx effects. Two Stx1-exposed greyhounds were analyzed for hemostatic changes prior to onset of clinical manifestations. Serial hemostasis studies after Stx1 challenge revealed trends of increased aPTT, fibrinogen levels, and prothrombin fragment 1+2, and appearance of abnormally large von Willebrand factor multimers. Three greyhounds were anticoagulated with lepirudin to maintain activated partial thromboplastin times (aPTT) >2.5-fold normal, followed by administration of Stx2 and observation of clinical responses. Among the 3 lepirudin-treated, Stx2-challenged greyhounds, one developed severe illness requiring euthanasia. Remarkably, 2 of the 3 greyhounds developed only hypersalivation and restlessness that resolved (P <.03 compared to 14 historical controls). These two greyhounds were clinically, hematologically and biochemically normal 74 hours after Stx administration, well beyond the time of euthanasia of any previous greyhound. This study suggests that greyhounds exposed to Stx develop procagulant changes similar to humans, and that thrombin may be a critical factor in the pathogenesis and treatment of Stx-HUS.
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, pharmacology, toxicology, Shiga toxin mediated hemolytic uremic syndrome, blood and lymphatic disease, infectious disease, urologic disease, chemically induced, microvascular thrombosis, vascular disease, hemostasis .

Shaw, M., R. Moutvic, M. Brooker, and I. Grossi (2003). **Evaluation of the effects of intermittent exposure to elevated inhaled co2 concentrations upon blood gas and hematologic parameters in the canine.** *Toxicological Sciences* 72(S-1): 296 ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, respiratory system, respiration, hematocrit, laboratory techniques, hematologic parameters, minute volume, peak inspiratory flow, tidal volume.

Skripchenko, A., A. Balch, A. Mackin, and S.J. Wagner (2007). **In vivo recovery and survival of red cells after photodynamic treatment with thiopyrylium and red light using a canine model.** *Vox Sanguinis* 92(2): 157-9. ISSN: 0042-9007.
NAL Call Number: 448.8 V94
Abstract: Recently, we have shown that thiopyrylium has robust inactivation capabilities against a broad spectrum of pathogens in the human red blood cell (RBC) suspensions while

retaining key RBC in vitro properties. The 24-h recovery and survival of canine red cells were measured upon autologus reinfusion of control and phototreated units. The 24-h recovery of control and phototreated RBCs was 75.7 +/- 6.4% and 87.5 +/- 8.5%, respectively. The time for 50% survival of labelled control RBCs was similar to that of phototreated group (206 +/- 58 h vs. 255 +/- 63 h, respectively). Results suggest that thiopyrylium phototreatment does not negatively affect canine RBC in vivo recovery.
Descriptors: aniline compounds pharmacology, blood preservation methods, erythrocytes drug effects, hemolysis drug effects, photosensitizing agents pharmacology, pyrans pharmacology, bacterial infections prevention and control, cell survival, decontamination methods, dogs, erythrocyte membrane drug effects, erythrocytes microbiology, erythrocytes virology, models, animal, virus diseases prevention and control.

Stokol, T. (2003). **Plasma D-dimer for the diagnosis of thromboembolic disorders in dogs.** *Veterinary Clinics of North America. Small Animal Practice* 33(6): 1419-35. ISSN: 0195-5616.
NAL Call Number: SF601.V523
Abstract: D-dimer is formed during thrombus formation when factor XIIIa crosslinks the terminal D-domains of fibrin. The D-dimer epitope is exposed when the thrombus is lysed by plasmin. Thus, D-dimer represents both thrombin and plasmin activation and is specific for fibrinolysis. D-dimer concentrations are increased in dogs with DIC or other thromboembolic disorders, but because D-dimer is an indicator of physiologic or pathologic fibrinolysis, values are elevated in other conditions associated with fibrinolysis, including orthopedic surgery, neoplasia, and internal hemorrhage. It can be used as an ancillary test for the diagnosis of DIC but is not recommended as a sole test for this purpose. D-dimer has the potential to be a useful laboratory test for the detection of pulmonary thromboembolism in dogs. Further studies are needed to determine the appropriate applications for this test in veterinary patients to aid in clinical decision making, treatment, and patient care.
Descriptors: D-dimer, thrombus formation, plasmin activation, thromboembolic disorders, orthopedic surgery, neoplasia, internal hemorrhage.

Tisherman, S.A. (2004). **Suspended animation for resuscitation from exsanguinating hemorrhage.** *Critical Care Medicine* 32(2 Suppl): S46-50. ISSN: 0090-3493.
Abstract: In dogs, isotonic saline at 0-4 degrees C, flushed into the aorta at a rate of 1-2 L/min, with drainage of the vena cava, can achieve deep to profound hypothermia of vital organs at a cooling rate of up to 3 degrees C per minute. This achieves preservation of viability of the organism during predictable durations of no flow: cardiac arrest of 15-20 mins at Tty of 30-35 degrees C, cardiac arrest of 30 mins at Tty of 25 degrees C, cardiac arrest of 60 mins at Tty of 15 degrees C, and cardiac arrest of 90 mins at Tty of 10 degrees C. So far, pharmacologic approaches have not resulted in any breakthrough effect on outcome above that achieved with hypothermia, except perhaps the antioxidant tempol. Additional studies of novel drugs and, perhaps, combination therapies remain warranted. The optimal fluids to have in the circulation during circulatory arrest and reperfusions need to be determined. As laboratory studies to optimize suspended animation proceed, clinical trials should be initiated. In addition, devices should be developed to facilitate induction of suspended animation, eventually in the field.

Descriptors: animal model, hypothermia, vital organs, circulatory arrest, suspended animation.

Varicoda, E.Y., L.F. Poli De Figueiredo, R.J.J. Cruz, L.E. Silva, and M. Rocha E Silva (2003). **Blood loss after fluid resuscitation with isotonic or hypertonic saline for the initial treatment of uncontrolled hemorrhage induced by spleen rupture.** *Journal of Trauma Injury Infection and Critical Care* 55(1): 112-117. ISSN: 1079-6061.

Abstract: Background: It has been suggested that fluid resuscitation for the prehospital management of hypotensive trauma victims increases bleeding. In a model of uncontrolled hemorrhage induced by complete splenic laceration with a hilar vascular injury, we hypothesized that small-volume hypertonic saline or large-volume lactated Ringer's solution may provide sustained hemodynamic benefits despite promoting increases in intra-abdominal bleeding. Methods: Forty anesthetized, spontaneously breathing dogs (18 +- 1 kg) underwent laparotomy. A suture line was placed around the spleen to produce a splenic rupture with hilar vascular injury by pulling the exteriorized lines after incision closure. Intra-abdominal blood loss was measured directly, immediately after the animal was killed. Dogs were randomly assigned to four groups (n = 10 per group): Untreated controls were killed 20 (CT20) or 40 (CT40) minutes after splenic rupture to measure blood loss directly. Treatment groups received (20 minutes after spleen rupture) lactated Ringer's (LR), 33 mL/kg over 15 minutes, or 7.5% NaCl/6% dextran 70 (HSD), 4 mL/kg over 4 minutes. Blood loss was measured 40 minutes after spleen rupture. Results: Mean arterial pressure dropped from an average value of 103 +- 3 mm Hg to 67 +- 5 mm Hg during the first 20 minutes and was partially restored afterward in all groups, with no significant differences between them. No resuscitation was associated with low cardiac output, whereas HSD restored and LR overshot baseline cardiac output. Intraabdominal blood loss was 30 +- 4, 38 +- 4, 43 +- 5, and 42 +- 5 mL/kg for groups CT20, CT40, HSD, and LR, respectively, with no statistical significance between groups. Conclusion: No-fluid resuscitation in uncontrolled hemorrhage from splenic rupture resulted in a low-flow state, whereas resuscitation with small volumes of HSD or large volumes of LR produced hemodynamic benefits without significant increases in bleeding.

Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, methods and techniques, hemorrhage, ascular disease, spleen rupture, blood and lymphatic disease, injury, fluid resuscitation, clinical techniques, therapeutic and prophylactic techniques.

Wu, M.H.D., Y. Kouchi, Y. Onuki, Q. Shi, H. Yoshida, S. Kaplan, R.F. Viggers, R. Ghali, and L.R. Sauvage (1995). **Effect of differential shear stress on platelet aggregation, surface thrombosis, and endothelialization of bilateral carotid-femoral grafts in the dog**. *Journal of Vascular Surgery* 22(4): 382-392. ISSN: 0741-5214.

Abstract: Purpose: The purpose of this study was to determine the effects of increased shear stress on the aggregability of platelets as they traverse a long, small-caliber (6 min) Dacron graft in the dog and on the surface thrombosis and endothelialization of such a graft. Methods: Each of nine dogs received bilateral carotid-femoral artery grafts, approximately 75 cm long, for 3 months; one graft of each pair had a distal femoral arteriovenous fistula to produce a higher shear rate than the contralateral graft. Platelet aggregation scores were determined on blood withdrawn from the external jugular vein and eta-m the proximal and

distal ends of the grafts in each animal. Graft flow rates, which were used in the computation of shear stress, and luminal pressure gradients through grafts were measured during surgery and specimen retrieval. Specimens were studied with light microscopy after hematoxylin and eosin and immunocytochemical staining and by scanning electron and transmission electron microscopy to evaluate the nature, composition, and thickness of the flow surface lining, as well as the transmural healing. Results: Two high-shear stress and two low-shear stress grafts occluded unilaterally; five dogs had bilaterally patent grafts, allowing comparative analyses. AR subjects had low platelet aggregability with aspirin. Platelet aggregation scores taken from proximal and distal ends of the grafts were not significantly different. The high-shear stress grafts had significantly more endothelial-like cell coverage (p lt 0.0371) than the low-shear stress grafts, less flow-surface thrombus (p lt 0.0056), and a thinner surface lining (p lt 0.0029), on both the neointima and pseudointima. Conclusions: In subjects with low platelet aggregation scores, long Dacron grafts do not elevate platelet aggregability of blood flowing through them. High-shear stress grafts have less flow surface thrombus, more endothelialization, and a thinner surface lining than do low-shear stress grafts.
Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, cell biology, methods and techniques, morphology, physiology, axillofemoral bypass, dacron graft, graft patency, intimal hyperplasia, surgical method.

Yu, S., Y. Ma, T. Xia, and S. Ma (1995). **Studies of action of rhodobrun roseum limpr on changes of red cell aggregation and yield-shear stress in dogs with acute experimental coronary occlusion**. *Zhongguo Zhongyao Zazhi* 20(7): 429-431, 449. ISSN: 1001-5302.
Abstract: Following acute occlusion of the left anterior descending coronary artery in dogs, significant increases were observed in the red cell aggregation index, yield-shear stress and red cell electrophoretic time in blood drained from ischemic area. When transfusion was performed with Rhodobrum roseum solution from the right femoral vein, significant rises of the above-said items were observed.
Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, cell biology, pharmacognosy, pharmacology, blood viscosity, myocardial ischemia.
Language of Text: Chinese.

Zaucha, J.M., C. Yu, G. Mathioudakis, K. Seidel, G. Georges, G. Sale, M.T. Little, B. Torok Storb, and R. Storb (2001). **Hematopoietic responses to stress conditions in young dogs compared with elderly dogs**. *Blood* 98(2): 322-327. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Clinical observations show that older patients do not tolerate high-dose chemoradiotherapy as well as younger patients. It is unclear whether this is due to age-related differences in their responses to hematopoietic injury or to differential toxicities to other organs. In the present study, 6 young (0.5 years) and 6 elderly (8 years) dogs were challenged with 7 repeated nonlethal doses of 50 or 100 cGy total body irradiation (TBI) each (total 550 cGy), and 21 days of recombinant canine granulocyte-colony stimulating factor (rcG-CSF) after the last TBI dose. Recoveries of absolute neutrophil, platelet, and lymphocyte counts after each TBI dose, responses to rcG-CSF treatment, and telomere lengths in neutrophils were compared before and after the study. No differences were found in recoveries

of neutrophils, platelets, or in responses to rcG-CSF among young and old dogs. In contrast, recoveries were suggestively worse in younger dogs. After rcG-CSF, platelet recoveries were poor in both groups compared with previous platelet recoveries (P<.01). Consequently, 2 old and 3 young dogs were euthanized because of persistent thrombocytopenia and bleeding. At the study's completion, marrow cellularities and peripheral blood counts of the remaining young and elderly dogs were equivalent. The telomere lengths in both groups were significantly reduced after the study versus beforehand (P=.03), but the median attritions of telomeres were not different. It was concluded that aging does not appear to affect hematopoietic cell recoveries after repeated low-dose TBI, suggesting that poor tolerance of radiochemotherapy regimens in older patients may be due to nonhematopoietic organ toxicities rather than age-related changes in hematopoietic stem cells reserves.
Descriptors: aging, pharmacology, radiation biology, blood and lymphatics, transport and circulation, thrombocytopenia, blood and lymphatic disease, radiochemotherapy, radiologic method, therapeutic method, bleeding, hematopoietic responses, stress conditions, total body irradiation.

Zhang, H., R. De Jongh, D. De Backer, S. Cherkaoui, B. Vray, and J.L. Vincent (2001). **Effects of alpha - and beta -adrenergic stimulation on hepatosplanchnic perfusion and oxygen extraction in endotoxic shock.** *Critical Care Medicine.* 29(3): 581-8. ISSN: 0090-3493.
Abstract: OBJECTIVE: To examine the effects of adrenergic stimulation on hepatosplanchnic perfusion, oxygen extraction, and tumor necrosis factor-alpha production during endotoxic shock. DESIGN: In vivo, prospective, randomized, controlled, repeated-measures, experimental study. SETTING: Experimental physiology laboratory in a university teaching hospital. SUBJECTS: Twenty-one anesthetized and mechanically ventilated dogs. INTERVENTIONS: An intrapericardial catheter was positioned. Catheters for blood sampling were inserted into the right femoral artery, hepatic vein, portal vein, and pulmonary artery. Ultrasonic flow probes were placed around the portal vein, the hepatic artery, the mesenteric artery, the left renal artery, and the left femoral artery. Animals received 2 mg/kg of Escherichia coli endotoxin, followed by fluid resuscitation. Seven dogs received intravenous isoproterenol (0.1 microg/kg x min(-1)), seven received phenylephrine (1 microg/kg x min(-1)), and seven served as controls. Thirty minutes later, cardiac tamponade was introduced to study organ perfusion and tissue oxygen extraction capabilities. MAIN RESULTS: The isoproterenol group had a higher cardiac index and stroke index and lower systemic vascular resistance than the other groups. The phenylephrine group had a higher arterial pressure but a lower cardiac index than the isoproterenol group. The isoproterenol group had a higher hepatic artery blood flow than the other groups and a higher portal and mesenteric flow than the control group. Liver and gut mucosal blood flow was greater in the isoproterenol than in the phenylephrine group. The isoproterenol group had a lower global critical oxygen delivery than the other groups (8.8 +/- 1.3 vs. 13.1 +/- 2.0 (control) and 11.8 +/- 3.3 mL/kg x min(-1) (phenylephrine); both p < .05) and a higher liver critical oxygen extraction ratio than the control group. Isoproterenol tended to attenuate, but phenylephrine significantly increased, blood tumor necrosis factor levels. CONCLUSIONS: During endotoxic shock, beta-stimulation can improve hepatosplanchnic perfusion and enhance tissue oxygen extraction capabilities, whereas alpha-stimulation does not. In addition, alpha-adrenergic stimulation can increase tumor necrosis factor levels.

Descriptors: endotoxic shock model, adrenergic stimulation, hepatosplanchnic perfusion, oxygen extraction, tumor necrosis factor-alpha production.

Zhang, X.B., T. Neff, R.K. Humphries, and H.P. Kiem (2003). **Retroviral overexpression of human hoxb4 confers an ex vivo growth advantage to cd34+ cells from dogs, baboons, macaques and humans.** *Blood* 102(11): 569A. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Over-expression of the human HoxB4 gene has been shown to induce ex vivo expansion and self-renewal of murine long term repopulating multilineage hematopoietic stem cells. Successful ex vivo expansion of stem cells has great potential for clinical cell therapy applications. Since mouse and human differ substantially with respect to stem cell biology, we have started to develop a large animal model to study the effect of HoxB4 on hematopoietic stem cells in a clinically more relevant experimental setup. We investigated if human HoxB4 enhances in vitro expansion of CD34+ cells from mobilized dog peripheral blood (PB), cytokine primed baboon and macaque bone marrow (BM), human cord blood (CB) and mobilized human PB. Baboon, macaque and human cells were cultured in IMDM/10%FCS in the presence of human TPO, SCF, Flt3-L, IL-6, IL-3 and G-CSF each at 100 ng/ml. Dog cells were cultured in human Dexter media with Flt3-L, canine SCF and canine G-CSF, each at 50 ng/ml. Enriched CD34+ cells were pre-stimulated for 2 days and then transduced twice with Phoenix-GALV or RD114 pseudotyped MSCV-HoxB4-ires-GFP or the control vector, MSCV-ires-YFP. Cells were maintained in suspension cultures. Cultures were split every week, and flow-cytometric analysis for GFP/YFP-expression and CFU assays were performed. After 4 weeks culture, the percentage of HoxB4-overexpressing dog cells increased from 30% to 76% (n=5), while YFP (mock)-transduced dog cells decreased from 53% to 30% (n=5) ($p<0.05$, paired T test). The same HoxB4-mediated growth advantage was observed for baboon (GFP from 29% to 63% and YFP from 33% to 26%) (n=4) ($p<0.05$) and macaque (GFP from 32% to 80% and YFP from 38% to 43%)(n=4) ($p<0.05$). In dog, macaque and baboon cells, HoxB4-overexpression resulted in an up to 28-fold expansion of CFUs compared with YFP-transduced control cells. Transduction with the HoxB4-vector also augmented total cell expansion 3 to 5-fold in suspension cultures of dog, baboon and macaque cells when compared with YFP-transduced controls ($p<0.05$). In human CB, HoxB4 overexpression induced a 2-fold augmented expansion in the number of CFUs relative to YFP control. Of note, flow cytometric analysis of liquid cultures did not show a difference in human cord blood cells (GFP from 81% to 53% and YFP from 93% to 56%) (n=3). In preliminary experiments we were unable to demonstrate a HoxB4 mediated in vitro growth advantage in human PB CD34+ cells. In conclusion, our data demonstrate that HoxB4 has an effect on CD34+ cells from dog, macaque and baboon. The effect on human PB cells is less pronounced than that on human CB cells. Our data indicate that either of the two non-human primates or the canine model can be used to investigate the effects of HoxB4 on hematopoietic stem cells in a clinically relevant model.
Descriptors: blood and lymphatics, transport and circulation, molecular genetics, biochemistry and molecular biophysics.

Immune System

Barrett, E.G., K. Rudolph, S.Z. Wang, B.A. Muggenburg, M. Nysus, K. Clarke, and C. Mccall (2002). **Epicutaneous sensitization with house dust mites leads to pulmonary immune responses in dogs.** *Journal of Allergy and Clinical Immunology* 109(1 Supplement): S35. ISSN: 0091-6749.
NAL Call Number: 448.8 J8236
Descriptors: biochemistry and molecular biophysics, immune system, chemical coordination and homeostasis, respiratory system, respiration, epicutaneous sensitization, pulmonary immunity, meeting abstract.

Bauer, T.R.J., K.E. Creevy, Y.C. Gu, L.M. Tuschong, R.E. Donahue, M.E. Metzger, L.J. Embree, T. Burkholder, J.D. Bacher, C. Romines, M.L.I. Thomas, L. Colenda, and D.D. Hickstein (2004). **Very low levels of donor cd18+ neutrophils following allogeneic hematopoietic stem cell transplantation reverse the disease phenotype in canine leukocyte adhesion deficiency**. *Blood* 103(9): 3582-3589. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Descriptors: large animal model, clinical immunology, human medicine, medical sciences, hematology, surgery, bacterial infection, infectious disease, leukocyte adhesion deficiency, blood and lymphatic disease, immune system disease, allogeneic hematopoietic stem cell transplantation, clinical techniques, gene therapy, genetic techniques, laboratory techniques, nonmyeloablative hematopoietic stem cell transplantation, disease phenotype.

Bauer, T.R.J., Y.C. Gu, K.E. Creevy, L.M. Tuschong, L. Embree, S.M. Holland, R.A. Sokolic, and D.D. Hickstein (2004). **Leukocyte adhesion deficiency in children and irish setter dogs.** *Pediatric Research* 55(3): 363-367. ISSN: 0031-3998.
NAL Call Number: RJ1.P4
Abstract: Children with the genetic immunodeficiency disease leukocyte adhesion deficiency, or LAD, develop life-threatening bacterial infections as a result of the inability of their leukocytes to adhere to the vessel wall and migrate to the sites of infection. Recently, the canine counterpart to LAD, known as canine leukocyte adhesion deficiency, or aaCLAD, has been described in Irish setter dogs. This review describes how the clinical phenotype of dogs with CLAD closely parallels that of children with the severe deficiency phenotype of LAD, thus enabling the CLAD dog to provide a disease-specific, large-animal model for testing novel hematopoietic stem cell and gene therapy strategies before their translation to children with LAD.
Descriptors: immune system, leukocyte adhesion deficiency syndrome, genetic disease, gene therapy, clinical techniques, genetic techniques, phenotype, animal model, genetic immunodeficiency disease leukocyte hematopoietic stem cell therapy.

Bethge, W.A., D.S. Wilbur, R. Storb, D.K. Hamlin, E.B. Santos, M.W. Brechbiel, D.R. Fisher, and B.M. Sandmaier (2003). **Selective t-cell ablation with bismuth-213-labeled anti-tcralpha-beta as nonmyeloablative conditioning for allogeneic canine marrow transplantation.** *Blood* 101(12): 5068-5075. ISSN: 0006-4971.

NAL Call Number: RB145.A1B57

Abstract: Two major immunologic barriers, the host-versus-graft (HVG) and graft-versus-host (GVH) reactions, have to be overcome for successful allogeneic hematopoietic cell transplantation. T cells were shown to be primarily involved in these barriers in the major histocompatibility complex identical setting. We hypothesized that selective ablation of T cells using radioimmunotherapy together with postgrafting immunosuppression would suffice to ensure stable allogeneic engraftment. We had described a canine model of non-myeloablative marrow transplantation in which host immune reactions were impaired by a single dose of 200 cGy total body irradiation (TBI), and both GVH and residual HVG reactions were controlled by postgraftifig immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP). Here, we substituted the alpha-emitter bismuth-213 (213Bi) linked to a monoclonal antibody (mAb) against T-cell receptor (TCR) alphabeta, using the metal-binding chelate diethylenetriaminepentaacetic acid (DTPA) derivative cyclohexyl-(CHX)-A", for 200 cGy TBI. Biodistribution studies using a gamma-emitting indium-111-labeled anti-TCRalphabeta mAb showed uptake primarily in blood, marrow, lymph nodes, spleen, and liver. Four dogs were treated with 0.13 to 0.46 mg/kg TCRalpha-beta mAb labeled with 3.7 to 5.6 mCi/kg (137-207 MBq/kg) 213Bi. The treatment was administered in 6 injections on days -3 and -2 followed by transplantation of dog leukocyte antigen-identical marrow on day 0 and postgrafting immunosuppression with MMF/CSP. The therapy was well tolerated except for elevations of transaminases that were transient in all but one of the dogs. No other organ toxicities or signs of graft-versus-host disease were noted. The dogs had prompt allogeneic hematopoietic engraftment and achieved stable mixed donor-host hematopoietic chimerism with donor contributions ranging from 5% to 55% after more than 30 weeks of follow up.

Descriptors: immune system, chemical coordination and homeostasis, methods and techniques, graft vs host disease, immune system disease, allogeneic marrow transplantation, clinical techniques, therapeutic and prophylactic techniques, radioimmunotherapy, immunologic techniques, laboratory techniques, selective t cell ablation.

Brady, C.A. and C.M. Otto (2001). **Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction.** *Veterinary Clinics of North America. Small Animal Practice* 31(6): 1147-1162. ISSN: 0195-5616.

NAL Call Number: SF601.V523

Abstract: Companion animals with sepsis and multiple organ dysfunction can be the most challenging of all patients to treat. Current research in humans and laboratory models offers some exciting insights into the pathophysiology behind some of our most frustrating clinical challenges. This article applies several current concepts to a clinical case of pancreatitis and secondary sepsis to illustrate some of the cardiovascular, immune, and coagulation abnormalities commonly seen.

Descriptors: sepsis, multiple organ dysfunction, treatment, common problems, pathophysiology.

Caminis, A., C. Diez Fernandez, and P. Prieto (1999). **Cell-surface expression of heat shock proteins in dog neutrophils after oxidative stress**. *Toxicology In Vitro* 13(3): 437-443. ISSN: 0887-2333.
NAL Call Number: RA1190.T692
Abstract: The effect of oxidative stress induced by different concentrations of hydrogen peroxide on dog neutrophils was studied. This effect was measured using dichlorofluorescein-diacetate (DCFH-DA) and by the cell surface membrane expression of heat shock protein (HSP) 27 kDa, HSP 72 kDa and HSP 90 kDa families. Hydrogen peroxide induced a concentration-dependent increase in DCFH oxidation (from 10-6 M to 10-4 M), and an increase in the cell surface expression of HSPs families. At a concentration of 10-4 M, the percentage of positive cells that showed an oxidation of DCFH was 94.7% +- 5.2 (n = 3). Only vitamin E (but not vitamin C) at a concentration of 0.5 mM was able to inhibit the intracellular oxidative stress induced by hydrogen peroxide. The percentage of positive cells that express these proteins after the treatment with hydrogen peroxide (10-4 M) was: 74% +- 3.5 for HSP 27, 72% +- 2.6 for HSP 72 and 73% +- 1.2 for HSP 90 (n = 3). This cell surface expression was not abolishedby either vitamin C or vitamin E. Localization of HSPs in plasma membrane is of immunological interest because they have been implicated in autoimmune diseases.
Descriptors: biochemistry and molecular biophysics, immune system, chemical coordination and homeostasis, metabolism, oxidative stress.

Casal, M., S. Ryan, J. Rhodes, and J. Scheidt (2003). **Immunological aspects of x-linked ectodermal dysplasia: a dog model for the human disease.** *American Journal of Human Genetics* 73(5): 454. ISSN: 0002-9297.
NAL Call Number: QH431.A1A54
Descriptors: molecular genetics, biochemistry and molecular biophysics, X linked ectodermal dysplasia, genetic disease, immune system disease, integumentary system disease, respiratory system disease, genetics, immunology, pathology, transmission, pulmonary disorders, respiratory system disease, respiratory tract infection, infectious disease, cytokine production, immune system defects, immunological aspects, systemic, localized humoral, cellular responses.

Chaprazov, T. (2006). **Changes in some clinical and laboratory indices in dogs with experimental Staphylococcus aureus sepsis.** *Bulgarian Journal of Veterinary Medicine* 9(1): 51-60. ISSN: 1311-1477.
Abstract: The study was conducted in 6 clinically healthy dogs that were experimentally infected via intravenous injection of 5 mL broth culture of a field Staphylococcus aureus strain (1.2x109 cells/mL). The dynamics of rectal temperature, heart and respiratory rates and haematological parameters (erythrocyte counts, haematocrit, haemoglobin, erythrocyte sedimentation rate, total and differential leukocyte counts, total protein, fibrinogen, bilirubin, urea, creatinine, pyruvate and lactate) were observed for 28-day period. It was observed

that after 2 h of post-infection an increase in body temperature, tachycardia and tachypnea occurred. Followed by a marked leukopenia with an increased leukocyte counts at the 24th h with a left shift were noticed. Statistically significant increased in the values of blood biochemical parameters were observed for fibrinogen and bilirubin, while the concentrations of pyruvate decreased. The levels of total protein, creatinine, urea and lactate remained stable without significant deviations during the entire period of the survey..
Descriptors: bilirubin, blood chemistry, body temperature, clinical aspects, creatinine, disease markers, erythrocytes, experimental infections, fibrinogen, hematocrit, hematology, hemoglobin, heart rate, lactic acid, leukocytes, leukopenia, pathogenesis, pyruvic acid, respiration, septicaemia, urea, dogs, *Staphylococcus aureus*.

Christopher, S.A., B. Chung, J. Kennedy, S. Krakowka, P.F. Moore, K.I. Weinberg, and P.J. Felsburg (2004). **Enhanced t cell regeneration following allogeneic bone marrow transplantation (bmt) in xscid dogs co-transplanted with il-7 transduced mesenchymal stem cells (msc)**. *FASEB Journal* 18(4-5): Abst. 560.4. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: immune system, chemical coordination and homeostasis, methods and techniques, lymphopenia, blood and lymphatic disease, allogenic bone marrow transplantation, clinical techniques, therapeutic and prophylactic techniques, gene therapy, genetic techniques, transfection, laboratory techniques, t cell regeneration, enhancement, thymopoiesis.

Creevy, K.E., T.R.J. Bauer, L.M. Tuschong, L.J. Embree, L. Colenda, K. Cogan, M.F. Starost, M.E. Haskins, and D.D. Hickstein (2003). **Canine leukocyte adhesion deficiency colony for investigation of novel hematopoietic therapies**. *Veterinary Immunology and Immunopathology* 94(1/2): 11-22. ISSN: 0165-2427.
NAL Call Number: SF757.2.V38
Abstract: The genetic immunodeficiency disease canine leukocyte adhesion deficiency (CLAD) was originally described in juvenile Irish Setters with severe, recurrent bacterial infections. CLAD was subsequently shown to result from a mutation in the leukocyte integrin CD18 subunit which prevents leukocyte surface expression of the CD11/CD18 complex. We describe the development of a mixed-breed CLAD colony with clinical features that closely parallel those described in Irish Setters. We demonstrate that the early identification of CLAD heterozygotes and CLAD-affected dogs by a combination of flow cytometry and DNA sequencing allows the CLAD-affected animals to receive life-saving antibiotic therapy. The distinct clinical phenotype in CLAD, the ability to detect CD18 on the leukocyte surface by flow cytometry, and the history of the canine model in marrow transplantation, enable CLAD to serve as an attractive large-animal model for the investigation of novel haematopoietic stem cell and gene therapy strategies.
Descriptors: diagnosis, DNA sequencing, flow cytometry, genetic disorders, heterozygotes, leukocyte disorders, leukocytes.

Felsburg, P.J., B.J. Hartnett, T.A. Gouthro, and P.S. Henthorn (2003). **Thymopoiesis and t cell development in common gamma chain-deficient dogs.** *Immunologic Research* 27(2-3): 235-245. ISSN: 0257-277X.

NAL Call Number: QR180.S88

Abstract: Our laboratory has identified an X-linked severe combined immunodeficiency (XSCID) in dogs that is the result of mutations in the common gamma chain (gammac) subunit of the interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Canine XSCID, unlike genetically engineered gammac-deficient mice, has a clinical and immunologic phenotype virtually identical to human XSCID, suggesting species-specific differences exist in the role of the gammac and its associated cytokines in mice in comparison to their role in humans and dogs. This review compares and contrasts thymopoiesis and postnatal T cell development in gammac-deficient (XSCID) dogs raised in a conventional environment, with gammac-deficient dogs raised in a gnotobiotic environment. Therapy to accelerate T cell regeneration following hematopoietic stem cell transplantation or gene therapy is also discussed.

Descriptors: cell biology, genetics, immune system, chemical coordination and homeostasis, methods and techniques, X linked severe combined immunodeficiency, genetic disease, immune system disease, gene therapy, clinical techniques, genetic techniques, laboratory techniques, therapeutic and prophylactic techniques, genetic engineering, hematopoietic stem cell transplantation, thymopoiesis.

Georges, G.E., R. Storb, J.M. Zaucha, A.G. Taranova, T. Gooley, and R.A. Nash (2003). **Il-2 does not enhance the conversion to complete donor chimerism following nonmyeloablative hematopoietic cell transplantation in dogs.** *Bone Marrow Transplantation* 31(11): 1027-1031. ISSN: 0268-3369.

Abstract: A dog model of stable mixed hematopoietic chimerism was established in which leukocyte-antigen-identical littermates receive nonmyeloablative total body irradiation before hematopoietic cell transplantation and postgrafting immunosuppression with mycophenolate mofetil and cyclosporine. Unmodified donor lymphocyte infusion (DLI) into stable mixed chimeras failed to increase donor chimerism, while DLI from donors sensitized to recipient minor-histocompatibility antigens promptly converted all recipients to complete donor chimerism. This established a model for studying approaches to enhance the graft-versus-host (GVH)-effect, a potential surrogate for graft-versus-leukemia activity. We asked if interleukin-2 (IL-2) given after unmodified DLI could result in reliable conversion to complete donor chimerism. IL-2, 4X105 IU/kg/day, was administered to six mixed chimeric dogs for 14 days. Four dogs received unmodified DLI with IL-2. At 20-40 weeks after DLI, all dogs remained mixed chimeras. For the two recipients of IL-2 only, mixed chimerism also remained unchanged. These results show that IL-2 given with DLI after nonmyeloablative transplantation in dogs is not effective in reliably converting mixed to complete donor chimerism.

Descriptors: immune system, chemical coordination and homeostasis, pharmacology, nonmyeloablative hematopoietic cell transplantation, clinical techniques, therapeutic and prophylactic techniques, total body irradiation, laboratory techniques, unmodified donor lymphocyte infusion, complete donor chimerism, graft vs host effect, immunosuppression, mixed donor chimerism.

Hammerberg, B. and A.K. Smith (2003). **Membrane-bound and soluble stem cell factor expression by skin cells during atopic dermatitis in dogs.** *Journal of Allergy and Clinical Immunology* 111(2 Abstract Supplement): S342-S343. ISSN: 0091-6749.
NAL Call Number: 448.8 J8236
Descriptors: cell biology, immune system, chemical coordination and homeostasis, integumentary system, chemical coordination and homeostasis, immunohistochemistry, immunologic techniques, laboratory techniques, reverse transcriptase polymerase chain reaction, genetic techniques.

Higgins, M.A., B.R. Berridge, B.J. Mills, A.E. Schultze, H. Gao, G.H. Searfoss, T.K. Baker, and T.P. Ryan (2003). **Gene expression analysis of the acute phase response using a canine microarray.** *Toxicological Sciences* 74(2): 470-484. ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Abstract: The safety of pharmaceuticals is typically assessed in the dog and rat prior to investigation in humans. As a result, a greater understanding of adverse effects in these preclinical testing species would improve safety assessment. Despite this need, there is a lack of tools to examine mechanisms and identify biomarkers in the dog. To address this issue, we developed an Affymetrix-based oligonucleotide microarray capable of monitoring the expression of thousands of canine genes in parallel. The custom canine array contains 22,774 probe sets, consisting of 13,729 canine and 9045 human-derived probe sets. To improve cross-species hybridization with human-derived probes, the detection region was moved from the variable 3' UTR to the more homologous coding region. Testing of this strategy was accomplished by comparing hybridization of naive dog liver RNA to the canine array (coding region design) and human U133A array (standard 3' design). Although raw signal intensity was greater with canine-specific probe sets, human-derived probes detected the expression of additional liver transcripts. To assess the ability of this tool to detect differential gene expression, the acute phase response was examined in beagle dogs given lipopolysaccharide (LPS). Hepatic gene expression 4 and 24 h post-LPS administration was compared to gene expression profiles of vehicle-treated dogs (n = 3/group). Array data was consistent with an acute inflammatory response, with transcripts for multiple cytokines and acute phase proteins markedly induced 4 h after LPS challenge. Robust changes in the expression of transcripts involved with glucose homeostasis, biotransformation, and extracellular matrix remodeling were observed 24 h post-dose. In addition, the canine array identified several potential biomarkers of hepatic inflammation. Strong correlations were found between gene expression data and alterations in clinical chemistry parameters such as serum amyloid A (SAA), albumin, and alkaline phosphatase (ALP). In summary, this new genomic tool successfully detected basal canine gene expression and identified novel aspects of the acute phase response in dog that shed new light on mechanisms underlying inflammatory processes.
Descriptors: immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, toxicology, affymetrix based oligonucleotide microarray, genetic techniques, laboratory techniques, canine microarray, gene expression analysis, acute phase response, biotransformation, canine genomics, extracellular matrix remodeling, glucose homeostasis, hepatic gene expression, inflammation, toxicogenomics.

Hogan, W.J., M.L. Sorror, R. Diaconescu, E. Zellmer, M.T. Little, and R. Storb (2003). **Marrow engraftment after nonmyeloablative conditioning followed by postgrafting immunosuppression with mycophenolate mofetil, sirolimus and cyclosporine in a canine model.** *Blood* 102(11): 396b. ISSN: 0006-4971.

NAL Call Number: RB145.A1B57

Abstract: Previous studies have demonstrated that postgrafting immunosuppression with cyclosporine (CSP) for 5 weeks combined with mycophenolate mofetil (MMF) for 4 weeks will allow durable donor engraftment after 200 cGy TBI but not after 100 cGy TBI. Similarly, a combination of CSP for 5 weeks combined with sirolimus (SRL) for 4 weeks can secure engraftment after 200 cGy. We sought to determine whether the combination of all three agents to the post-grafting immunosuppression regimen would enhance durable engraftment after non-myeloablative conditioning in a canine model at 100 cGy TBI. Four dogs received 100 cGy TBI followed by a dog leukocyte antigen (DLA) identical marrow graft and post-grafting immunosuppression with MMF (10mg/kg sc bid, day 0 to 27), SRL (0.05 mg/d sc, day 0 to 27) and CSP (10 mg/kg po bid, day-1 to +35). All dogs showed initial engraftment with a median of 5% donor representation in both the granulocyte and lymphocyte fractions at the completion of immunosuppression. Three dogs went on to reject their grafts at a median of 10 (range 9-12) weeks and all three had autologous reconsitiution without severe or prolonged cytopenias. The fourth dog remains engrafted with 6% donor representation in both granulocyte and mononuclear lineages at 5 weeks. The regimen was well tolerated, all dogs remain alive and well, none experienced significant hepatic or renal dysfunction throughout the peritransplant period despite high CSP and SRL levels consistent with a pharmacokinetic interaction between SRL and CSP. Dose reductions were performed as necessary to maintain therapeutic levels of both CSP and SRL. Gastrointestinal toxicity predominated with anorexia, diarrhea and weight loss which was transient. Mild myelosuppression was observed with median (range) absolute neutrophil count (ANC) nadirs of 3.3 (2.1-4.1)X109/L and median (range) platelet nadirs of 34 (9-72)X109/L respectively. We conclude that the addition of MMF to SRL/CSP is associated with acceptable toxicity but rates of durable engraftment are not increased beyond that achieved by SRL/CSP alone. It is likely that 200 cGy TBI represents a threshold for conditioning below which engraftment cannot be secured by intensification of post-grafting immunosuppression alone. Alternative strategies to further reduce the intensity of conditioning may include the use of peripheral blood derived stem cell products or promotion of tolerance to donor cells prior to HCT by co-stimulatory blockade or antimetabolite blockade after pretransplant exposure to donor cells.

Descriptors: blood and lymphatics, transport and circulation, immune system, chemical coordination and homeostasis, pharmacology, absolute neutrophil count, histology and cytology techniques, laboratory techniques, nonmyeloablative conditioning, clinical techniques, therapeutic and prophylactic techniques, marrow engraftment.

Horton, P.J., W.J. Hawthorne, S. Walters, T. Patel, G.J. Stewart, R.D. Allen, and J.R. Chapman (2008). **Tolerance induction in a large-animal model using total lymphoid irradiation and intrathymic bone marrow.** *Transplantation* 86(12): 1830-6.

NAL Call Number: QP89.T73

Abstract: BACKGROUND: Immunological unresponsiveness of T cells to alloantigen can

be induced by intrathymic injection of donor-specific antigen in small-animal models. Intrathymic tolerance to vascularized grafts in large animals has not previously been reported. METHODS: Thirty-two dogs were allocated into dog leukocyte antigen DP locus allele (class II)-matched donor-recipient pairs. Female recipients were paired with male donors. Tissue typing was based on restriction fragment length polymorphism. Recipients were given 18 Gy total lymphoid irradiation in 16 fractions (1.125 Gy each) over 4 weeks. Thoracotomy after the 6th fraction permitted perithymic (n=4) or intrathymic (n=4) injection of donor bone marrow (BM) or intrathymic injection of saline (n=5). Another group received intravenous peripheral BM infusion (n=3). Fifty days postthoracotomy recipients underwent bilateral nephrectomy and donor-specific kidney transplantation. Acute rejection, suspected when serum creatinine was more than 600 mumol/L or urea was more than 40 mmol/L, was confirmed histologically. Full-thickness skin grafts followed more than 100 days posttransplantation. Tissue samples were taken for Y-chromosome polymerase chain reaction. RESULTS: One intrathymic (25%) and three perithymic (75%) BM recipients developed tolerance to renal allografts. Three intrathymic BM recipients rejected after 27, 32, and 54 days and one perithymic BM recipient rejected after 42 days. All recipients given peripheral BM or saline had rejected by 29 and 38 days, respectively. All recipients surviving more than 100 days posttransplantation, accepted donor specific and rejected dog leukocyte antigen-DP locus allele (class II) identical third-party skin grafts. Polymerase chain reaction detected intrathymic but not hematopoietic chimerism in sex-mismatched pairs. CONCLUSIONS: Fractionated total lymphoid irradiation and perithymic or intrathymic donor-specific BM induced tolerance to renal and skin allografts without inducing hematopoietic chimerism.
Descriptors: histocompatibility testing methods, immune tolerance, isoantigens pharmacology, kidney transplantation immunology, lymphatic system radiation effects, t lymphocytes immunology, bone marrow cells pathology, bone marrow cells physiology, bone marrow transplantation, computer simulation, dogs, histocompatibility antigens class ii immunology, lymphatic system immunology, models, animal, nephrectomy, polymorphism, restriction fragment length, skin transplantation immunology.

Huang, J.C., W.T. Lu, B.R. Hsu, C.H. Kuo, S.H. Fu, H.M. Chen, N.K. Yao, and J.H. Juang (2003). **Canine islet isolation, cryopreservation, and transplantation to nude mice.** *Chang Gung Medical Journal* 26(10): 722-8.
Abstract: BACKGROUND: Successful human islet transplantation has led to insulin independence in type 1 diabetes. Dogs constitute an animal model for preclinical studies. We present our recent experience in canine islet isolation, cryopreservation and transplantation. METHODS: Twenty-seven pancreases from mongrel dogs, weighing 9-31 kg, were removed. Each pancreas was digested with collagenase, and then purified by density gradients. Islet number and purity were counted, and the viability of isolated islets was assessed in vitro by static incubation, perifusion study and in vivo transplantation into nondiabetic or diabetic nude mice. Additionally. freshly isolated islets were cryopreserved for 1 week, and then studied in vitro. RESULTS: The islet yield and purity were 121,000 +/- 135,000 IEQ per pancreas and 81.4 +/- 1.2%, respectively. The stimulation index (insulin release in 300 mg/dl glucose/insulin release in 100 mg/dl glucose) of the isolated islets was 6.6 +/- 1.9 (N = 7), and first and second phases of insulin secretion were demonstrated during perifusion study. After 1-week cryopreservation, the islet number decreased from 1,000 to 540 (N

= 1) and insulin content decreased from 50.95 to 39.23 microg/150 islets (N = 1). These islets maintained their insulin response to high glucose. Four weeks after transplantation, the grafts showed abundant beta-cells and significant insulin content. Normoglycemia was achieved in 14 of 23 diabetic recipients after transplantation with 2,000 freshly isolated islets. CONCLUSION: Canine islets isolated at our laboratory were viable and maintained their physiological function both in vitro and in vivo.
Descriptors: animal model, preclinical studies, canine islet isolation, cryopreservation, transplantation, human islet transplantation, diabetes.

Kemming, G., J.B. Messick, W. Mueller, G. Enders, F. Meisner, S. Muenzing, H. Kisch Wedel, A. Schropp, C. Wojtczyk, K. Packert, K. Messmer, and E. Thein (2004). **Can we continue research in splenectomized dogs? Mycoplasma haemocanis: old problem - new insight**. *European Surgical Research* 36(4): 198-205. ISSN: 0014-312X.
Descriptors: cardiovascular system, transport and circulation, infection, Mycoplasma haemocanis infection, bacterial disease, diagnosis, therapy, blood smear, diagnostic techniques, laboratory techniques, specific polymerase chain reaction, genetic techniques.

Kosaka, T., Y. Kaneko, Y. Nakada, M. Matsuura, and S. Tanaka (1996). **Effect of chitosan implantation on activation of canine macrophages and polymorphonuclear cells after surgical stress**. *Journal of Veterinary Medical Science* 58(10): 963-967. ISSN: 0916-7250.
NAL Call Number: SF604.J342
Abstract: The effect of cotton type chitosan implantation under the skin on the immunological response mediated by macrophages and whole blood was evaluated chemiluminescence (CL) in dogs. The number of white blood cells was significantly decrease until 120 hr after operation in the control group (p lt 0.05), while chitosan implantation increased the number of white blood cells, particularly neutrophils, from 24 to 96 hr after implantation (p lt 0.05). The CL response of whole blood in the control group seemed to be reduced at 48 and 96 after operation (p lt 0.05), but in the chitosan groups it maintained higher activity until 120 hr after implantation (p lt 0.05). The macrophage activity measured by CL assay in the control group was markedly decreased form 24 to 120 hr after operation, and that for the 5 mg/kg chitosan group was also decreased at 24 and 48 hr after implantation (p lt 0.05), although high activity was observed from 72 to 120 hr after implantation (p lt 0.05). Neither 5 mg/kg nor 10 mg/kg chitosan groups showed and reduction in CL response of macrophages after operation, and the 20 mg/kg chitosan group retained high CL response of macrophages until 120 hr after operation (p lt 0.05). These findings suggest that chitosan may be and efficacious and useful immunopotentiator for preventation of immunosuppression after surgery.
Descriptors: chemiluminescence, implantation, macrophages, stress, chitosan, nonspecific immunostimulation, surgery, blood and lymphatics, transport and circulation, cell biology, immune system, chemical coordination and homeostasis, physiology , veterinary medicine, medical sciences, analytical method, blood and lymphatics, implantation, immunosuppressant method, macrophage , polymorphonuclear cell, surgical stress.

Kuhr, C.S., M. Yunusov, G. Sale, C. Loretz, and R. Storb (2007). **Long-term tolerance to kidney allografts in a preclinical canine model.** *Transplantation* 84(4): 545-7. ISSN: 0041-1337.
NAL Call Number: QP89.T73
Abstract: Durable immune tolerance supporting vascularized allotransplantation offers the possibility of extending graft survival and avoiding harmful complications of chronic immunosuppression. Immune tolerance to renal allografts was induced in a preclinical canine model through engraftment of donor hematopoietic cells using a combination of low-dose total body irradiation and a short course of immunosuppression. Subsequently, donor renal allografts were transplanted accompanied by bilateral native nephrectomies. With 5-year follow up, we found normal renal function in all recipients and no histological evidence of acute or chronic rejection. This tolerance does not extend universally to donor skin grafts, however, with two of four animals rejecting delayed donor skin grafts. Hematopoietic chimerism produces durable and robust immune tolerance to kidney allografts, although incomplete tolerance to donor skin grafting.
Descriptors: graft survival immunology, kidney transplantation immunology, transplantation tolerance immunology, dogs, immune tolerance immunology, immunosuppression, kidney pathology, kidney physiology, kidney transplantation pathology, kidney transplantation physiology, models, animal, skin transplantation immunology, time factors.

Lesnikova, M., M.C. Jensen, A. Bukovsky, A. Nikitine, B. Thomasson, J. Morris, R.F. Storb, H.P. Kiem, R.A. Nash, and G.E. Georges (2003). **Resistance to mycophenolate mofetil (mmf) after lentiviral transduction of canine t cells with a mutant impdh vector.** *Blood* 102(11): 499B. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Several clinical studies of adoptive immunotherapy with genetically modified (GM) donor T cells infused after allogeneic hematopoietic cell transplantation (HCT) have shown limited in vivo function of the ex vivo expanded T cells. Multiple factors including duration of ex vivo cell culture, immunogenicity of the transgene, lack of a selective advantage for the GM T cells and insufficient preclinical data in large animal models may have impaired successful clinical translation of this approach. To help address these problems, we constructed a self-inactivating, replication incompetent lentiviral vector expressing a (Thr-333fwdarwIle, Ser-351fwdarwTyr) trans-dominant mutant inosine monophosphate dehydrogenase II (IMPDH*), which renders transduced T cells resistant to MMF with intact de novo guanosine synthesis. MMF administration after infusion of IMPDH* transduced T cells would inhibit host immune responses to the GM T cells and provide a proliferative advantage for transduced T cells. Lentiviral vector transduction can reduce the time in culture since T cell proliferation is not required. In preparation for in vivo studies in the dog model of allogeneic HCT, we first confirmed function of the IMPDH* vector in immortalized T cell lines and then optimized conditions for lentiviral transduciton of fresh, primary dog T cells to achieve 20-30% transduction efficiency. Replication incompetent, VSV-G pseudotyped IMPDH* lentiviral vector, pRRLsin.cPPT.MSCV.IMPDH*.Wpre, was prepared from transiently transfected 293T cells. Immortalized dog T lymphocyte CLGL-90 cells were transduced with IMPDH* lentiviral vector and selected in 1 muM MMF for 14 days. Transduced cells were cloned by limiting dilution and assayed for MMF resistance. All IMPDH* CLGL-90 clones were uniformly resistant to MMF 0.1 to 10 muM, compared

to control CLGL cells. Quantitative TaqMan PCR assay with lentiviral-specific primers showed transduced CLGL clones had up to 3 lentiviral vector insertion copies per clone. Next, fresh CD3+ T cells were isolated from dog peripheral blood with immunomagnetic selection (Miltenyi) or plastic adherence to >90% purity. Cells were cultured with IL-2 (10 IU/mL) and IL-7 (20 ng/mL) for 72 hours. T cells were transduced once at an MOI of 20 with the spinoculation method. Transduced cells were stimulated after 24 hours with MHC-mismatched dendritic cells (DC) (10:1 responder: stimulator ratio) and selected in 0.5 muM MMF 2 days later. After 2nd stimulation with DCs, cells were assessed for proliferation with 3H-thymidine uptake. In the presence of MMF, IMPDH* transduced cells had 3-fold increased proliferation over nontransduced control T cells. In summary, lentiviral vector expressing trans-dominant mutant IMPDH* rendered transduced dog T cells resistant to MMF. These results establish the IMPDH* vector as a tool to confer in vivo resistance to MMF. We are planning adoptive immunotherapy studies with infusion of IMPDH* transduced donor T cells into recipient dogs treated with MMF after allogeneic HCT to determine the feasibility of in vivo selection of GM T cells.
Descriptors: blood and lymphatics, transport and circulation, immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, pharmacology, adoptive immunotherapy, clinical techniques, immunologic techniques, laboratory techniques, therapeutic and prophylactic techniques, allogeneic hematopoietic cell transplantation, clinical techniques, lentivirus transduction, drug resistance mechanism, host immune response, transduction efficiency.

Lester, T., M. Passage, R. Yang, C. Tanaka, V. Anand, J. Lemontt, and E. Kakkis (2003). **Reduction of the immune response to therapeutic enzyme replacement therapy in a canine model of a lysosomal storage disorder.** *Journal of Inherited Metabolic Disease* 26(Supplement 2): 143. ISSN: 0141-8955.
NAL Call Number: RC627.8.J68
Descriptors: enzymology, biochemistry and molecular biophysics, immune system, chemical coordination and homeostasis, metabolism, pharmacology, canine mucopolysaccharidosis I, lysosomal storage disorder, connective tissue disease, genetic disease, metabolic disease, therapy, enzyme replacement therapy, clinical techniques, therapeutic and prophylactic techniques, drug regimen.

Linfert, D., T. Chowdhry, and H. Rabb (2009). **Lymphocytes and ischemia-reperfusion injury.** *Transplantation Reviews* 23(1): 1-10.
NAL Call Number: QP89.T7
Abstract: Ischemia reperfusion injury (IRI) is a common and important clinical problem in many different organ systems, including kidney, brain, heart, liver, lung, and intestine. IRI occurs during all deceased donor organ transplants. IRI is a highly complex cascade of events that includes interactions between vascular endothelium, interstitial compartments, circulating cells, and numerous biochemical entities. It is well established that the innate immune system, such as complement, neutrophils, cytokines, chemokines, and macrophages participate in IRI. Recent data demonstrates an important role for lymphocytes, particularly T cells but also B cells in IRI. Lymphocytes not only participate in augmenting injury responses after IRI, but could also be playing a protective role depending on the cell type and stage of

injury. Furthermore, lymphocytes appear to be participating in the healing response from IRI. These new data open the possibility for lymphocyte targeted therapeutics to improve the short and long term outcomes from IRI.
Descriptors: b lymphocytes immunology, organ transplantation adverse effects, reperfusion injury immunology, t lymphocytes immunology, cd4 positive t lymphocytes immunology, cadaver, dogs, immunosuppressive agents therapeutic use, mice, mice, scid immunology, models, animal, reperfusion injury physiopathology, reperfusion injury prevention and control, retrospective studies, tissue donors.

Maeda, S., K. Ohmori, N. Yasuda, K. Kurata, M. Sakaguchi, K. Masuda, K. Ohno, and H. Tsujimoto (2004). **Increase of CC chemokine receptor 4-positive cells in the peripheral CD4 cells in dogs with atopic dermatitis or experimentally sensitized to Japanese cedar pollen.** *Clinical and Experimental Allergy* 34(9): 1467-1473. ISSN: 0954-7894.
Abstract: BACKGROUND: Since dogs frequently develop allergic diseases, similar to those in humans, dogs represent a possible animal model for allergy in humans. In human atopic dermatitis (AD), CC chemokine receptor 4 (CCR4) has been shown to play an important role in the development of allergic inflammation of AD; however, the association between allergic reaction and CCR4 is not well understood in dogs. OBJECTIVE: To examine CCR4 expression in peripheral blood CD4+ cells in dogs that had AD and were experimentally sensitized with Japanese cedar pollen. MATERIALS AND METHODS: Peripheral blood mononuclear cells (PBMCs) were isolated from 17 dogs with AD. The proportion of CCR4+ cells in peripheral blood CD4+ cells (CCR4/CD4) was evaluated by flow cytometry and compared with that in 10 healthy dogs. Similarly, in dogs that were experimentally sensitized to Japanese cedar pollen antigen, the proportion of CCR4/CD4 was examined pre- and post-sensitization. RESULTS: The proportion of CCR4/CD4 in dogs with AD was 40.3+/-3.3%, which was significantly higher than that in normal dogs (23.6+/-4.3%) (P<0.01). In the experimentally sensitized dogs, the proportion of CCR4/CD4 was 25.4+/-2.6% at pre-sensitization and it was significantly increased (29.8+/-2.9%) at post-sensitization (P<0.01). CONCLUSION: The proportion of CCR4+ cells in peripheral blood CD4+ cells was measured in dogs with allergic conditions. The present findings indicate that CCR4+ cells may be involved in the pathogenesis of allergy in dogs as in humans.
Descriptors: animal model, allergies, atopic dermatitis, cedar pollen, chemokine receptor 4 (CCR4).

Marsella, R. and C.F. Nicklin (2001). **Sulphido-leukotriene production from peripheral leukocytes and skin in clinically normal dogs and house dust mite positive atopic dogs**. *Veterinary Dermatology* 12(1): 3-12. ISSN: 0959-4493.
NAL Call Number: SF901.V47
Descriptors: atopy, leukotrienes, leukocytes, skin, skin diseases, allergies, allergic reactions, house dust mites, dermatophagoides, atopy, dermatitis, leukocytes, skin, leukotrienes, pruritus, IgE, blood serum, allergens.
Language of Text: Summaries in German, Spanish, French.

Marsella, R., C.F. Nicklin, S. Saglio, and J. Lopez (2004). **Investigation on the effects of topical therapy with 0.1% tacrolimus ointment (Protopic) on intradermal skin test reactivity in atopic dogs**. *Veterinary Dermatology.* 15(4): 218-224. ISSN: 0959-4493.
NAL Call Number: SF901.V47
Descriptors: atopy, dermatitis, dermatological agents, drug therapy, ointments, pharmacology, skin diseases, skin tests, topical application.
Language of Text: Summaries in German; Spanish; French.

Petersen, S.M., M. Gendelman, K.M. Murphy, M. Torbenson, R.J. Jones, J.E. Althaus, G. Stetten, C. Bird, and K.J. Blakemore (2007). **Use of T-cell antibodies for donor dosaging in a canine model of in utero hematopoietic stem cell transplantation.** *Fetal Diagnosis and Therapy* 22(3): 175-9. ISSN: 1015-3837.
Abstract: AIM: Microchimerism following canine in utero hematopoietic stem cell transplantation (IUHSCT) development of T-cell dosing regimens. OBJECTIVE: To investigate the use of anti-T-cell antibodies for cell dosing of the donor graft in a canine model of IUHSCT. STUDY DESIGN: Canine IUHSCT was performed by ultrasound-guided intraperitoneal injection in days 35-38 of fetal canines with CD34(+) cells at doses of 4.5 x 10(8) to 1.3 x 10(9) cells/kg and T cells (CD3(+) CD5(+)) at doses of 8 x 10(6) to 8.8 x 10(8) cells/kg. Postnatal studies included tissue histology and polymerase chain reaction-based chimerism analysis. RESULTS: Term survival was 86-100%. Microchimerism (0-2%) was detected in five of eight recipients in multiple tissues. Histopathology revealed no evidence of graft-versus-host disease (GVHD). CONCLUSION: Canine IUHSCT is a useful model to investigate the role of donor T cells in engraftment and GVHD. IUHSCT at early gestational ages with high doses of donor T cells in the graft yields microchimerism in multiple tissues without GVHD. (c) 2007 S. Karger AG, Basel.
Descriptors: fetal therapies methods, fetal tissue transplantation methods, hematopoietic stem cell transplantation methods, animals, newborn, antilymphocyte serum administration and dosage, base sequence, dna primers genetics, dogs, fetal tissue transplantation immunology, graft survival immunology, models, animal, t lymphocytes immunology, tissue donors, transplantation chimera genetics, transplantation chimera immunology.

Pumarola, M., P.F. Moore, and G.D. Shelton (2004). **Canine inflammatory myopathy: analysis of cellular infiltrates**. *Muscle and Nerve* 29(6): 782-789. ISSN: 0148-639X.
Abstract: Inflammatory myopathies (IMs) occur relatively frequently in dogs, and, with the exception of masticatory muscle myositis (MMM), have not been characterized. This study analyzed the distribution and types of cellular infiltrates in 21 cases of generalized IM, 3 cases of focal IM (MINIM), and 1 case with features of both generalized and focal IM, using a panel of monoclonal antibodies to cell surface markers. In generalized IM, mononuclear cells showed an endomysial and perimysial distribution with invasion of non-necrotic fibers similar to human IM. T lymphocytes with T-cell receptor (TCR)alphabeta predominated. Distinct differences were seen in MMM including prominent B-cell infiltration, dendritic cells and macrophages in greater numbers than T cells, and numerous T cells with TCR-gammadelta. Thus, generalized IM and MMM appear to be distinct diseases with different mechanisms. Canine generalized IM may be an important animal model for human IM.
Descriptors: immune system, chemical coordination and homeostasis, infection, muscular

system, movement and support, veterinary medicine, medical sciences, dermatomyositis, connective tissue disease, integumentary system disease, muscle disease, polymyositis, connective tissue disease, muscle disease.

Ramiro, M.J., J.J. Zarate, T. Hanke, D. Rodriguez, J.R. Rodriguez, M. Esteban, J. Lucientes, J.A. Castillo, and V. Larraga (2003). **Protection in dogs against visceral leishmaniasis caused by leishmania infantum is achieved by immunization with a heterologous prime-boost regime using dna and vaccinia recombinant vectors expressing lack.** *Vaccine* 21(19-20): 2474-2484. ISSN: 0264-410X.
NAL Call Number: QR189.V32
Abstract: A heterologous prime-boost vaccination regime with DNA and recombinant vaccinia virus (rVV) vectors expressing relevant antigens has been shown to enhance specific cellular immune responses and to elicit protection against a variety of pathogens in animal models. In this paper, we describe the effectiveness of the prime-boost strategy by immunizing dogs with a plasmid carrying the gene for the LACK antigen from Leishmania infantum (DNA-LACK) followed by a booster with a rVV containing the same gene (rVV-LACK). Thereafter, animals were challenged with L. infantum to induce visceral leishmaniasis (VL). In the vaccinated dogs as compared with the controls, the outcome of the infection after challenge with a high inoculum (108) of L. infantum stationary promastigotes was assessed by tissue parasite load, specific anti-Leishmania antibody production, cytokine level and development of clinical signs of leishmaniasis. We observed a 60% protection against infection in dogs immunized by DNA-LACK prime/rVV/-LACK boost while two doses of DNA-LACK did not elicit protection against the disease. The interleukin 4 (IL-4), interferon gamma (IFNgamma) and IL-12 (p40 subunit) cytokine mRNA expression profiles in PBMC as well as lymphocyte proliferative response and the IgG2/IgG1 ratios specific for LACK suggest that in vaccinated animals there is triggering of cellular immune responses. This type of DNA/rVV prime/boost immunization approach may have utility against visceral leishmaniasis-in dogs.
Descriptors: immune system, methods and techniques, parasitology, visceral leishmaniasis, parasitic disease, heterologous prime boost regime immunization, clinical techniques, therapeutic and prophylactic techniques.

Shengwu, Z., L. Qingfeng, J. Hao, J. Banich, F. Kaiding, C. Benson, W. Huiyong, Z. Danning, G. Bing, L. Qinxiu, T. Lujia, Z. Tao, L. Yuping, and Z. Tisheng (2007). **Developing a canine model of composite facial/scalp allograft transplantation.** *Annals of Plastic Surgery* 59(2): 185-194. ISSN: 0148-7043.
Abstract: The study developed a model of composite facial and scalp allograft transplantation in canines. Dog cadavers were used for anatomy study. Three types of autotransplantations and 2 types of allotransplantations were performed. Cyclosporin A and methylprednisolone or prednisone were given for immunosuppression. Two long-term-surviving dogs with autologous facial transplantation developed leakage of salivary secretions. In the allotransplantation group (n = 5), 1 dog presented rejection at 28 postoperative days but was successfully treated and survived long term (>402 days); 1 dog died of pulmonary infection at 29 postoperative days; 3 dogs survived (>252, >222, and >201 days). Serial electromyelogram studies revealed progressive improvement of the function of the orbicularis oculi

muscle. The study indicated that the unilateral superior half of the composite facial and scalp, including one third of the inferior tarsal plate and palpebral conjunctiva (type IV flap) allograft transplantation model, was an ideal model for the study of facial allotransplantation.
Descriptors: face surgery, models, animal, scalp transplantation, tissue transplantation methods, dogs.

Suter, S.E., T.A. Gouthro, P.A. Mcsweeney, R.A. Nash, M.E. Haskins, P.J. Felsburg, and P.S. Henthorn (2004). **Isolation and characterization of pediatric canine bone marrow cd34+ cells**. *Veterinary Immunology and Immunopathology* 101(1-2): 31-47. ISSN: 0165-2427.
NAL Call Number: SF757.2.V38
Descriptors: animal models, bone marrow, characterization, genetic disorders, hematopoiesis, isolation, transplantation, blood and lymphatics, transport and circulation, immune system, chemical coordination and homeostasis, methods and techniques, veterinary medicine, medical sciences, bone marrow transplantation, clinical techniques, therapeutic and prophylactic techniques, gene therapy, clinical techniques, genetic techniques, laboratory techniques, therapeutic and prophylactic techniques, gene transfer, liquid suspension cultures, culturing techniques, methylcellulose assay, bioassay techniques.

Tang, L., T. Morales, K.L. Boroughs, K.C. Lo Keiser, K. Sellins, K. Stedman, C. Mccall, and M.J. Mcdermott (2003). **Expression and characterization of recombinant canine il-13 receptor alpha2 protein and its biological activity in vitro.** *Molecular Immunology* 39(12): 719-727. ISSN: 0161-5890.
NAL Call Number: 448.3 Im62
Abstract: Our previous study showed that recombinant canine IL-13 (rcaIL-13) stimulated production of allergen-specific IgE in vitro by peripheral blood mononuclear cells (PBMC) from flea allergen-sensitized dogs. This has also been demonstrated using human IL-13 (huIL-13) and PBMC isolated from human allergy patients. The stimulatory activity of rcaIL-13 was specifically inhibited by a fusion protein of the extracellular domain of canine IL-13Ralpha2 and the Fc fragment of canine IgG heavy chain (rcaIL-13Ralpha2-Fc). In this communication, we report the construction and expression of a non-fused recombinant extracellular domain of canine IL-13Ralpha2 (rcaIL-13Ralpha2) in an E. coli expression system. The E. coli expressed rcaIL-13Ralpha2 was isolated in inclusion bodies, then solubilized in buffer containing denaturants and reducing agents. After refolding and purification, the biological activity of rcaIL-13Ralpha2 was found in the monomer fraction resulting from gel filtration and ion exchange chromatographies. Biological activity of purified rcaIL-13Ralpha2 was demonstrated by the specific inhibition of rcaIL-13 activity in a TF-1 cell proliferation assay. Additionally, rcaIL-13Ralpha2 was found to be active in neutralizing rcaIL-13 induced upregulation of IgE mRNA levels in PBMCs of 'high IgE' dogs, which have been bred to exhibit a predisposition for high IgE production and are used as a model for allergic asthma. The data confirm our previous report that the regulatory effects of IL-13 on IgE production in canine PBMCs are similar to those reported in humans. Thus, allergic dogs, such as the 'high IgE' producing dogs, may be excellent models for research on IgE-mediated diseases in humans.
Descriptors: cell biology, immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, allergic asthma, cell proliferation assay,

histology and cytology techniques, laboratory techniques, gel filtration, genetic techniques, ion exchange chromatography, chromatographic techniques.

Ting, S.S., S. Christopher, U. Choi, J. Deleon, G. Linton, N. Whiting Theobald, K. Yamashita, M.L. Harry, and P. Felsburg (2003). **In vivo gene transfer by intravenous injection of RD114-pseudotyped mfgs-gammac-ires-gfphmgmt achieves myeloid and lymphoid marking in XSCID dogs.** *Blood* 102(11): 249A-250A. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Dogs are an informative large animal model for hematopoietic stem cell therapies (transplantation or gene therapy). Relevent to the current study are dogs with mutant common cytokine receptor gamma chain (gammac) that have clinical phenotype similar to human X-linked severe combined immnunodeficiency (XSCID). Restoration of immune function in children with XSCID was achieved by ex vivo transduction of marrow stem cells with retrovirus vector encoding normal gammac. However, lymphoid malignancy occurred in 2 of 11 children at two to three years following gene therapy. This appeared to be associated with insertional mutagenesis activation of LMO2. The contributory role of unregulated expression of gammac transgene remains unclear. Of note is that the leukemias occurred in two patients who were youngest infants at time of gene therapy. Malignancies have not been seen with gene therapy correction of murine XSCID, but it is possible that leukemogenesis requires a longer period than the lifetime of mice. Gene therapy of XSCID dogs may provide an opportunity for prolonged followup required to see leukemogenesis. Efficient ex vivo retroviral gene transfer to hematopoietic stem cells using murine oncoretrovirus vectors requires growth factor mediated cell division, which induces cell differentiation and loss of homing and self-renewal capabilities. Recently, sustained marking of leukocytes has been reported following intravenous administration of ultrafiltration concentrated amphotropic envelope pseudotyped murine retrovirus vector for gene therapy of canine mucosaccharidosis VII (O'Malley et al., Molecular Therapy 7:S82, 2003). In the current study we used intravenous administration of the RD114 pseudotyped murine retrovirus vector MFGS-gammac-IRES-eGFPhMGMT* to three day old XSCID dogs to transduce hematopoietic stem cells in vivo, achieving marking of blood cells. This may prove to be a useful large animal model to observe and study long term effects that might arise. The vector encodes canine gc but also expresses downstream of an IRES element a reporter GFP fused to human P140K mutant methyl guanine methyl transfersase (MGMT*). This fusion protein confers both green fluorescence and benzyl guanine resistance. RD114 MFGS-gammac-IRES-GFPhMGMT* derived from FLYRD18 was concentrated 10 fold by tangential flow ultrafiltration/diafiltration, and further concentrated by ultracentrifugation. Three newborn XSCID dogs received 1.2X107 infectious units of resuspended virus intravenously twice a day for 2-3 days. GFP expression was first evident in small numbers of myeloid and lymphoid cells by initial flow cytometry assessment of peripheral blood at 10 days following the last injection. At 4 weeks lymphocyte counts in all three dogs were above 1500/mul. 7-21% of lymphocytes and 0.08-0.1% of myeloid cells were GFP positive. Preliminary studies using LAM-PCR demonstrated multiple insertion events in blood cells. Similar analysis in specific cellular subtypes is in progress. We demonstrate that direct intravenous administration of concentrated RD114 pseudotyped MFGS-gammac-IRES-GFPhMGMT* oncoretroviral vector achieves marking of both lymphoid and myeloid compartments with enhanced marking of the lymphoid com-

partment relative to the myeloid compartment. This is associated with steadily improving lymphocyte counts and polyclonal insertion pattern. We will monitor integrant pattern and clinical profile of these animals.

Descriptors: blood and lymphatics, transport and circulation, immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, lymphoid malignancy, blood and lymphatic disease, immune system disease, neoplastic disease, genetics, gene therapy, clinical techniques, genetic techniques, laboratory techniques, therapeutic and prophylactic techniques, gene transfer, ultrafiltration, laboratory techniques, immune function, leukemogenesis.

Trepanier, L.A. (2004). **Idiosyncratic toxicity associated with potentiated sulfonamides in the dog**. *Journal of Veterinary Pharmacology and Therapeutics* 27(3): 129-138. ISSN: 0140-7783.

NAL Call Number: SF915.J63

Abstract: Idiosyncratic toxicity to potentiated sulfonamides occurs in both humans and dogs, with considerable clinical similarities. The syndrome in dogs can consist of fever, arthropathy, blood dyscrasias (neutropenia, thrombocytopenia, or hemolytic anemia), hepatopathy consisting of cholestasis or necrosis, skin eruptions, uveitis, or keratoconjunctivitis sicca. Other manifestations seen less commonly include protein-losing nephropathy, meningitis, pancreatitis, pneumonitis, or facial nerve palsy. The pathogenesis of these reactions is not completely understood, but may be due to a T-cell-mediated response to proteins haptenated by oxidative sulfonamide metabolites. Our laboratory is working on tests to characterize dogs with possible idiosyncratic sulfonamide reactions, to include ELISA for anti-drug antibodies, immunoblotting for antibodies directed against liver proteins, flow cytometry for drug-dependent anti-platelet antibodies, and in vitro cytotoxicity assays. The management of idiosyncratic sulfonamide toxicity involves client education to identify clinical signs early and allow rapid drug discontinuation, supportive care to include possibly ascorbate and glutathione precursors, and avoidance of subsequent re-exposure. It is important to realize that only antimicrobial sulfonamides, such as sulfamethoxazole, sulfadiazine, and sulfadimethoxine, share this clinical syndrome. There is no evidence for cross-reactivity with drugs that have different underlying structures but share a sulfonamide moiety, such as acetazolamide, furosemide, glipizide, or hydrochlorothiazide.

Descriptors: adverse effects, antibodies, clinical aspects, dosage effects, drug allergies, drug toxicity, pathogenesis, reviews, sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfonamides, T lymphocytes, treatment, pharmacology, elisa, immunologic techniques, laboratory techniques, cytotoxicity assay, bioassay techniques, flow cytometry.

Weck, A.L.d., P. Mayer, B. Stumper, B. Schiessl, and L. Pickart (1997). **Dog allergy, a model for allergy genetics**. *International Archives of Allergy and Immunology* 113(1/3): 55-57. ISSN: 1018-2438.

NAL Call Number: RC583.I57

Abstract: Experimental sensitization in dogs has revealed that the capacity to produce high levels of IgE against a variety of allergens (high IgE responders), an essential characteristic of the atopic state, is a genetic trait inherited in a dominant manner. In high IgE responder dogs spontaneous development of IgE to inhaled allergens, such as house dust mites [usually Dermatophagoides spp.], on the other hand, represents an apparent phenotype very similar

to that observed in human atopic families. The full potential of the high IgE response gene appears to be fulfilled only under some conditions such as early and repeated exposition to allergens. It is, therefore, quite possible that the true phenotype of human atopy would also be inherited in a dominant fashion, but not constantly expressed. This would explain why the increase in the prevalence of allergic diseases started long before the environmental factors currently accused could have been at play. This hypothesis, which can be verified experimentally, has important implications for the future of allergy.
Descriptors: IgE, genetics, allergic reactions, house dust mites, disease models, laboratory animals, arthropod allergies, dogs, Dermatophagoides, Arachnida, Acari.

Weyer, J., C.E. Rupprecht, J. Mans, G.J. Viljoen, and L.H. Nel (2007). **Generation and evaluation of a recombinant modified vaccinia virus Ankara vaccine for rabies.** *Vaccine* 25(21): 4213-4222. ISSN: 0264-410X.
NAL Call Number: QR189.V32
Abstract: Modified vaccinia virus Ankara (MVA) has become a vaccine vector of choice for recombinant vaccine development. A MVA-based rabies vaccine would be advantageous for use as a vaccine for dogs (and wildlife), particularly if it proves innocuous and efficacious by the oral route. Here, the generation and immunological testing of a recombinant MVA expressing a rabies virus glycoprotein gene is described. In a murine model, higher dosages of recombinant MVA were needed to induce equivocal immune responses as with Vaccinia Copenhagen or Vaccinia Western Reserve recombinants, when administered by a parenteral route. The MVA recombinant was not immunogenic or efficacious when administered per os in naive mice. The ability of the recombinant MVA to induce anamnestic responses in dogs and raccoons was also investigated. Recombinant MVA boosted humoral immune responses in these animals when administered peripherally, but not when administered orally.
Descriptors: antigens, viral immunology, glycoproteins immunology, rabies prevention and control, rabies vaccines immunology, vaccines, synthetic immunology, vaccinia virus immunology, viral envelope proteins immunology, antibodies, viral, antigens, viral genetics, cell line, chickens, cricetinae, dogs, glycoproteins genetics, immunologic memory, mesocricetus, mice, mice, inbred balb c, models, animal, neutralization tests, rabies vaccines genetics, rabies virus genetics, rabies virus immunology, raccoons, vaccines, synthetic genetics, vaccinia virus genetics, viral envelope proteins genetics.

Yeh, H.I., Y.J. Lai, Y.N. Lee, Y.J. Chen, Y.C. Chen, C.C. Chen, S.A. Chen, C.I. Lin, and C.H. Tsai (2003). **Differential expression of connexin43 gap junctions in cardiomyocytes isolated from canine thoracic veins.** *Journal of Histochemistry and Cytochemistry* 51(2): 259-266. ISSN: 0022-1554.
NAL Call Number: 381 J8222
Abstract: We investigated the phenotypic features of cardiomyocytes, including the gap junctions, in the myocardial sleeve of thoracic veins. Single cardiomyocytes, isolated from the canine pulmonary veins (PV) and superior vena cava (SVC) using digestive enzymes, were examined by immunoconfocal microscopy using antisera against connexin43 (Cx43), Cx40, and other cell markers. The results showed that isolated cardiomyocytes displayed rod shapes of various sizes, ranging from <50 mum to >200 mum in length, and all the cells expressed alpha-actinin and vinculin. Gap junctions made of various amounts of Cx43 and Cx40 were

found at the cell borders. These two connexins were extensively co-localized. Comparison between the thoracic veins showed that cells of the SVC contained more Cx43 gap junctions (total Cx43 gap junctions area per cell surface area, 4.0+-0.2% vs 1.5+-0.2%; p<0.01). In addition, for single-nucleus cells, those from the PV were longer (103.7+-3.6 vs 85.0+-3.1 mum; p<0.01) but narrower (14.4+-0.5 vs 16.9mu0.9 mum; p<0.01). In conclusion, canine thoracic veins contain cardiomyocytes with differences in shape and gap junctions, suggesting that the electrical conduction properties may be different between the thoracic veins.
Descriptors: cardiovascular system, transport and circulation, cell biology, immunoconfocal microscopy, imaging and microscopy techniques, immunologic techniques, laboratory techniques.

Yuasa, K., M. Yoshimura, N. Urasawa, S. Ohshima, J.M. Howell, A. Nakamura, T. Hijikata, Y. Miyagoe Suzuki, and S. Takeda (2007). **Injection of a recombinant AAV serotype 2 into canine skeletal muscles evokes strong immune responses against transgene products.** *Gene Therapy* 14(17): 1249-1260. ISSN: 0969-7128.
Abstract: Using murine models, we have previously demonstrated that recombinant adeno-associated virus (rAAV)-mediated microdystrophin gene transfer is a promising approach to treatment of Duchenne muscular dystrophy (DMD). To examine further therapeutic effects and the safety issue of rAAV-mediated microdystrophin gene transfer using larger animal models, such as dystrophic dog models, we first investigated transduction efficiency of rAAV in wild-type canine muscle cells, and found that rAAV2 encoding beta-galactosidase effectively transduces canine primary myotubes in vitro. Subsequent rAAV2 transfer into skeletal muscles of normal dogs, however, resulted in low and transient expression of beta-galactosidase together with intense cellular infiltrations in vivo, where cellular and humoral immune responses were remarkably activated. In contrast, rAAV2 expressing no transgene elicited no cellular infiltrations. Co-administration of immunosuppressants, cyclosporine and mycophenolate mofetil could partially improve rAAV2 transduction. Collectively, these results suggest that immune responses against the transgene product caused cellular infiltration and eliminated transduced myofibers in dogs. Furthermore, in vitro interferon-gamma release assay showed that canine splenocytes respond to immunogens or mitogens more susceptibly than murine ones. Our results emphasize the importance to scrutinize the immune responses to AAV vectors in larger animal models before applying rAAV-mediated gene therapy to DMD patients.
Descriptors: dependovirus genetics, gene therapy adverse effects, genetic vectors adverse effects, muscle, skeletal immunology, muscular dystrophy, animal therapy, muscular dystrophy, duchenne therapy, base sequence, calmodulin genetics, cyclosporine administration and dosage, dogs, dystrophin genetics, dystrophin metabolism, gene therapy methods, genetic engineering, genetic vectors genetics, immunosuppressive agents administration and dosage, injections, intramuscular, interferon gamma immunology, lymphocyte activation, mice, mice, inbred c57bl, models, animal, molecular sequence data, muscle fibers, skeletal immunology, muscle fibers, skeletal virology, muscular dystrophy, animal immunology, muscular dystrophy, duchenne immunology, parvoviridae infections immunology, rna, messenger analysis, reverse transcriptase polymerase chain reaction, species specificity, t lymphocytes, cytotoxic immunology, transduction, genetic methods, transgenes, beta galactosidase genetics.

Molecular Genetics

Baker, S.M., L. Karlsson, and R.L. Thurmond (2003). **Cloning, expression, purification, and activity of dog (canis familiaris) and monkey (saimiri boliviensis) cathepsin s.** *Protein Expression and Purification* 28(1): 93-101. ISSN: 1046-5928.
NAL Call Number: QP551.P695818
Abstract: Cathepsin S is the key protease responsible for the removal of the invariant chain from MHC class II molecules and, as such, has attracted much attention as a target for developing immunosuppressive drugs. To help in testing candidate compounds, the monkey (Saimiri boliviensis) and dog (Canis familiaris) cathepsin S cDNAs have been cloned. The monkey cDNA sequence encodes a 330 amino acid protein with 95% homology to human cathepsin S. The dog cDNA sequence encodes a 331 amino acid protein with 91% homology to human cathepsin S. The amino acid differences do not have a major effect on the hydrolysis of the substrate Z-VVR-AMC, but may affect the substrate specificity. As for human and bovine cathepsin S, activity against Z-VVR-AMC extends into the neutral pH range. These parameters are important for understanding the role of cathepsin S in different species and for testing inhibitors in animal models of autoimmunity.
Descriptors: enzymology, biochemistry and molecular biophysics, genetics, immune system, chemical coordination and homeostasis, methods and techniques, amino acid sequence, peptide sequence, autoimmunity .

Beard, B.C., K.A. Keyser, G.D. Trobridge, L.J. Peterson, D.G. Miller, M. Jacobs, R. Kaul, and H.P. Kiem (2007). **Unique integration profiles in a canine model of long-term repopulating cells transduced with gammaretrovirus, lentivirus, or foamy virus.** *Human Gene Therapy* 18(5): 423-34. ISSN: 1043-0342.
Abstract: Recent advances have allowed for improved retrovirus-mediated gene transfer, and therapeutic benefits have been described in patients. These successes have shown the potential of hematopoietic stem cell (HSC) gene therapy, but treatment-related leukemia and benign expansion of gene-modified clones have shifted the attention toward safety. The delayed onset of adverse events in gene therapy clinical trials emphasizes the importance of long-term integration site studies in large animal models. We have addressed safety by characterizing the genomic location of 555 integration sites of the three most commonly used integrating retroviral vectors, that is, gammaretrovirus, lentivirus, and foamy virus, in long-term repopulating cells from dogs. Gammaretroviral integrants showed the most significant frequency of occurrence very close (<2.5 kb) to transcription start sites, but a substantial portion of all three retroviral integrants were within 50 kb. Importantly, gammaretroviral integrants were found more frequently in and near proto-oncogenes, suggesting this retroviral system may be the most prone to adverse gene activation. These data suggest that gammaretroviral vectors may have the highest intrinsic risk, but also emphasize that no vector system can be defined as "safe" based solely on integration profile.
Descriptors: gammaretrovirus genetics, lentivirus genetics, spumavirus genetics, transduction, genetic, virus integration genetics, base sequence, cpg islands, dna primers genetics,

dogs, gene therapy adverse effects, gene therapy methods, genetic vectors, models, animal, proto oncogenes, repetitive sequences, nucleic acid, safety.

Beard, B.C. and H.P. Kiem (2009). **Canine models of gene-modified hematopoiesis.** *Methods in Molecular Biology Clifton, N.J.* 506: 341-61. ISSN: 1064-3745.
Abstract: Large animal models have played a crucial role in the development of gene therapy protocols. A significant advantage of large animal models over rodent models includes the ability to more easily translate protocols developed in large animals to humans. For gene therapy applications, nonhuman primates and canines have been the main large animal models. Canines have the advantage that there are disease models available, e.g., hemolytic anemia (pyruvate kinase deficiency), leukocyte adhesion deficiency, severe combined immunodeficiency (XSCID), storage diseases, and others. In addition, all three major integrating virus systems, i.e., gammaretrovirus-, HIV-derived lenti- and foamy virus vectors are able to efficiently transduce canine hematopoietic cells. Here we describe protocols developed for efficient transduction of canine hematopoietic repopulating cells.
Descriptors: hematopoiesis genetics, models, animal, antigens, cd34 immunology, cells, cultured, dogs, flow cytometry, gene therapy, genetic vectors, hematopoietic stem cells immunology, retroviridae genetics, transduction, genetic.

Breen, M. (2008). **Canine cytogenetics: from band to basepair.** *Cytogenetic and Genome Research* 120(1-2): 50-60. ISSN: 1424-8581.
NAL Call Number: QH431 .C95
Abstract: Humans and dogs have coexisted for thousands of years, during which time we have developed a unique bond, centered on companionship. Along the way, we have developed purebred dog breeds in a manner that has resulted unfortunately in many of them being affected by serious genetic disorders, including cancers. With serendipity and irony the unique genetic architecture of the 21st century genome of Man's best friend may ultimately provide many of the keys to unlock some of nature's most intriguing biological puzzles. Canine cytogenetics has advanced significantly over the past 10 years, spurred on largely by the surge of interest in the dog as a biomedical model for genetic disease and the availability of advanced genomics resources. As such the role of canine cytogenetics has moved rapidly from one that served initially to define the gross genomic organization of the canine genome and provide a reliable means to determine the chromosomal location of individual genes, to one that enabled the assembled sequence of the canine genome to be anchored to the karyotype. Canine cytogenetics now presents the biomedical research community with a means to assist in our search for a greater understanding of how genome architectures altered during speciation and in our search for genes associated with cancers that affect both dogs and humans. The cytogenetics 'toolbox' for the dog is now loaded. This review aims to provide a summary of some of the recent advancements in canine cytogenetics. Copyright 2008 S. Karger AG, Basel.
Descriptors: genetic disorders, cancer, animal models, canine genome, chromosomal location, gene sequence

Casal, M., S. Ryan, J. Rhodes, and J. Scheidt (2003). **Immunological aspects of x-linked ectodermal dysplasia: a dog model for the human disease.** *American Journal of Human Genetics* 73(5): 454. ISSN: 0002-9297.
NAL Call Number: QH431.A1A54
Descriptors: molecular genetics, biochemistry and molecular biophysics, X linked ectodermal dysplasia, genetic disease, immune system disease, integumentary system disease, respiratory system disease, genetics, immunology, pathology, transmission, pulmonary disorders, respiratory system disease, respiratory tract infection, infectious disease, cytokine production, immune system defects, immunological aspects, systemic, localized humoral, cellular responses.

Chuah, M.K.L., G. Schiedner, L. Thorrez, B. Brown, M. Johnston, V. Gillijns, S. Hertel, N. Van Rooijen, D. Lillicrap, D. Collen, T. Vandendriessche, and S. Kochanek (2003). **Therapeutic factor viii levels and negligible toxicity in mouse and dog models of hemophilia a following gene therapy with high-capacity adenoviral vectors.** *Blood* 101(5): 1734-1743. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: High-capacity adenoviral (HC-Ad) vectors expressing B-domain-deleted human or canine factor VIII from different liver-specific promoters were evaluated for gene therapy of hemophilia A. Intravenous administration of these vectors into hemophilic FVIII-deficient immunodeficient SCID mice (FVIIIKO-SCID) at a dose of 5X109 infectious units (IU) resulted in efficient hepatic gene delivery and long-term expression of supraphysiologic FVIII levels (exceeding 15 000 mU/mL), correcting the bleeding diathesis. Injection of only 5X107 IU still resulted in therapeutic FVIII levels. In immunocompetent hemophilic FVIII-deficient mice (FVIIIKO), FVIII expression levels peaked at 75 000 mU/mL but declined thereafter because of neutralizing anti-FVIII antibodies and a cellular immune response. Vector administration did not result in thrombocytopenia, anemia, or elevation of the proinflammatory cytokine interleukin-6 (IL-6) and caused no or only transient elevations in serum transaminases. Following transient in vivo depletion of macrophages before gene transfer, significantly higher and stable FVIII expression levels were observed. Injection of only 5X106 HC-Ad vectors after macrophage depletion resulted in long-term therapeutic FVIII levels in the FVIIIKO and FVIIIKO-SCID mice. Intravenous injection of an HC-Ad vector into a hemophilia A dog at a dose of 4.3X109 IU/kg led to transient therapeutic canine FVIII levels that partially corrected whole-blood clotting time. Inhibitory antibodies to canine FVIII could not be detected, and there were no signs of hepatotoxicity or of hematologic abnormalities. These results contribute to a better understanding of the safety and efficacy of HC-Ad vectors and suggest that the therapeutic window of HC-Ad vectors could be improved by minimizing the interaction between HC-Ad vectors and the innate immune system.
Descriptors: blood and lymphatics, transport and circulation, genetics, molecular genetics, biochemistry and molecular biophysics, hemophilia A, blood and lymphatic disease, genetic disease, gene therapy, genetic techniques, laboratory techniques.

Cox, M.L., G.E. Lees, C.E. Kashtan, and K.E. Murphy (2003). **Genetic cause of X-linked Alport syndrome in a family of domestic dogs**. *Mammalian Genome.* 14(6): 396-403. ISSN: 0938-8990.

NAL Call Number: QL737.R638M68

Abstract: Alport syndrome is a hereditary disease of type IV (basement membrane) collagens that occurs spontaneously in humans and dogs. In the human, X-linked Alport syndrome (XLAS) is caused by mutations in COL4A5, resulting in absence of type IV collagen alpha 5 chains from the glomerular basement membrane (GBM) of affected individuals. The consequence of this defect is progressive renal failure, for which the only available treatments are dialysis and transplantation. Recent studies support the prospect of gene transfer therapy for Alport syndrome, but further development of required technologies and demonstration of safety and efficacy must be accomplished in a suitable animal model. We previously identified and have propagated a family of mixed-breed dogs with an inherited nephropathy that exhibits the clinical, immunohistochemical, pathological, and ultrastructural features of human XLAS. To identify the causative mutation, COL4A5 cDNAs from normal and affected dogs were sequenced in their entirety. Sequence analyses revealed a 10-bp deletion in exon 9 of affected dogs. This deletion causes a frame-shift that results in a premature stop codon in exon 10. Characterization of the causative mutation was followed by development of an allele-specific test for identification of dogs in this kindred that are destined to develop XLAS.

Descriptors: alleles, amino acid sequences, codons, collagen, complementary DNA, deletions, DNA sequencing, exons, genetic disorders, hereditary diseases, kidney diseases, mutations, nucleotide sequences, renal failure, X chromosome, dogs.

Creevy, K.E., T.R.J. Bauer, L.M. Tuschong, L.J. Embree, L. Colenda, K. Cogan, M.F. Starost, M.E. Haskins, and D.D. Hickstein (2003). **Canine leukocyte adhesion deficiency colony for investigation of novel hematopoietic therapies**. *Veterinary Immunology and Immunopathology* 94(1/2): 11-22. ISSN: 0165-2427.

NAL Call Number: SF757.2.V38

Abstract: The genetic immunodeficiency disease canine leukocyte adhesion deficiency (CLAD) was originally described in juvenile Irish Setters with severe, recurrent bacterial infections. CLAD was subsequently shown to result from a mutation in the leukocyte integrin CD18 subunit which prevents leukocyte surface expression of the CD11/CD18 complex. We describe the development of a mixed-breed CLAD colony with clinical features that closely parallel those described in Irish Setters. We demonstrate that the early identification of CLAD heterozygotes and CLAD-affected dogs by a combination of flow cytometry and DNA sequencing allows the CLAD-affected animals to receive life-saving antibiotic therapy. The distinct clinical phenotype in CLAD, the ability to detect CD18 on the leukocyte surface by flow cytometry, and the history of the canine model in marrow transplantation, enable CLAD to serve as an attractive large-animal model for the investigation of novel haematopoietic stem cell and gene therapy strategies.

Descriptors: diagnosis, DNA sequencing, flow cytometry, genetic disorders, heterozygotes, leukocyte disorders, leukocytes.

Ellinwood, N.M., P.S. Henthorn, U. Giger, and M.E. Haskins (2003). **Mucopolysaccharidosis type iiib: identification of the causative mutation in the canine model.** *American Journal of Human Genetics* 73(5): 449. ISSN: 0002-9297.
NAL Call Number: QH431.A1A54
Descriptors: enzymology, biochemistry and molecular biophysics, molecular genetics, biochemistry and molecular biophysics, mucopolysaccharidosis type IIIB, connective tissue disease, genetic disease, metabolic disease

Ford, M.M., R. Bragadottir, E. Rakoczy, and K. Narfstrom (2003). **Long - term visual behavior correlates with functional electroretinographic assessment after gene transfer in rpe65 - / - dogs**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*
Abstract: Purpose: To assess the long-term effects of subretinal rAAV.RPE65 gene transfer on functional vision in RPE65-/- dogs. Methods: Five dogs homozygous for the RPE65 null mutation and 2 unaffected, visually normal control dogs were included. Affected animals had been treated subretinally with 70 - 100 mul of rAAV.RPE65 gene construct (2 X 1012 particles/ml) in the right eye (OD), and 0 - 100 mul of rAAV.GFP (2 X 1010 transforming units/ml) in the left eye (OS). Treatment for control dogs was 75 - 100 mul of the latter OD and 100 mul of BSS OS. Evaluations from pre-surgical and follow-up bilateral full-field electroretinograms (ERGs) 6 mo post-surgery were obtained. Objective assessment of functional vision was performed 3 and 6 mo post-operatively by counting the number of collisions made by the dogs as they negotiated a maze of obstacles in dim and day light conditions. Vision in individual eyes was also assessed 6 mo post-surgery. Results: Three mo after gene therapy there was a higher number of collisions in dim light than in day light ($p<0.008$) among affected dogs; a difference not evident 6 mo post-operatively. In day light conditions, no difference was noted between control and affected animals at 3 or 6 mo. In dim light, affected dogs had a higher number of collisions than control dogs at 3 ($p<0.004$) but not 6 mo post-operatively. Fewer collisions ($p<0.1$) were noted in day and dim light when only OD was exposed compared with exposure of only OS in the affected dogs. Post-surgery, high intensity scotopic stimuli and 30 Hz flicker ERG amplitudes were elevated ($p<0.04$) over pre-operative recordings in OD, and elevated over post-operative recordings in OS as well ($p<0.032$). Further, post-operative single flash photopic b-wave amplitudes for OS were increased over pre-operative values ($p<0.05$). Conclusions: Progressive improvement in functional binocular and monocular (OD) vision up to 6 mo after gene transfer was found by objective behavioral testing. The long-term visual improvement correlated with a significant increase in post-operative ERG amplitudes, mainly in OD but also with measurable effects in OS.
Descriptors: methods and techniques, molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, functional electroretinography, laboratory techniques, gene transfer, genetic techniques, visual behavior.

Ford, M., R. Bragadottir, P.E. Rakoczy, and K. Narfstrom (2003). **Gene transfer in the rpe65 null mutation dog: relationship between construct volume, visual behavior and electroretinographic (erg) results.** *Documenta Ophthalmologica* 107(1): 79-86. ISSN: 0012-4486.

Abstract: In vivo gene transfer in a large group of RPE65 null mutation dogs have been recently performed. The present study was aimed at determining, through visual behavioral and electroretinographic (ERG) testing, if there is a volume effect of the gene construct administered. Eleven Beagle-Briard dogs homozygous for the RPE65 null mutation and two unaffected control dogs were included. Affected animals were unilaterally treated with either a high (70-100 mul; N=6) or a low volume (30-60 mul; N=5) of subretinally injected rAAV. RPE65 construct, at the age of 4 months to 2.5 years. Fellow eyes were treated with a subretinal injection of rAAV.GFP or sham operated and used as internal controls. Retinal function was measured pre- and 10-12 weeks post-surgically, using simultaneous bilateral full-field flash ERGs. A significant improvement in all ERG responses studied was identified for the high volume treated group compared to pre-surgical parameters. A significant improvement for the high intensity scotopic a-wave response for the low volume rAAV.RPE65 treated group was also found. Objective and subjective dim and day light visual maze testing, in eight of the affected treated animals, and the two control dogs, revealed better vision in daylight than in dim light for all animals. Vision in dogs treated with the high volume of gene construct was significantly better in day light than in dim light. No significant difference was noted between day and dim light testing for the control group or those animals treated with a low volume of the gene construct. Significantly better vision was noted in the control group when compared with the low volume group under dim light conditions, and the high volume group under day light conditions. No significant difference in functional vision could be identified between the high volume treated animals and control animals in day light conditions. These findings support the hypothesis that functional vision is improved by subretinal rAAV.RPE65 injection in a volume-dependent manner.
Descriptors: methods and techniques, molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, electroretinogram, clinical techniques, diagnostic techniques, in vivo gene transfer, genetic techniques, laboratory techniques, gene transfer, visual behavior.

Green, S.L., D.M. Bouley, M.J. Pinter, L.C. Cork, and G.T. Vatassery (2001). **Canine motor neuron disease: clinicopathologic features and selected indicators of oxidative stress**. *Journal of Veterinary Internal Medicine* 15(2): 112-119. ISSN: 0891-6640.
NAL Call Number: SF601.J65
Abstract: Hereditary canine spinal muscular atrophy (HCSMA) is an inherited motor neuron disease affecting a kindred of Brittanies. We have examined the clinicopathologic abnormalities in 57 animals with HCSMA, including 43 affected adult dogs and 14 homozygote pups. We also measured selected biochemical indices of oxidative stress: serum vitamin E (alpha-tocopherol) and Se concentrations; serum concentrations of Cu, Zn, Mg, and Fe; and total superoxide dismutase and glutathione peroxidase activities in red blood cells. Dogs with HCSMA had the following abnormalities: regenerative anemia, hypoglobulinemia, hypochloremia, and abnormally high creatine kinase and liver alkaline phosphatase activities. Serum Cu concentration was significantly (P = .01) increased in adult dogs with HCSMA compared to control dogs. Serum vitamin E concentrations tended to be lower in adult dogs with HCSMA compared to controls, and were significantly (P = .01) lower in homozygote pups compared to control pups.
Descriptors: veterinary medicine, medical sciences, neural coordination, hereditary canine

spinal muscular atrophy, nervous system disease, motor neuron disease, muscle disease, clinicopathologic features, oxidative stress.

Higgins, M.A., B.R. Berridge, B.J. Mills, A.E. Schultze, H. Gao, G.H. Searfoss, T.K. Baker, and T.P. Ryan (2003). **Gene expression analysis of the acute phase response using a canine microarray.** *Toxicological Sciences* 74(2): 470-484. ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Abstract: The safety of pharmaceuticals is typically assessed in the dog and rat prior to investigation in humans. As a result, a greater understanding of adverse effects in these preclinical testing species would improve safety assessment. Despite this need, there is a lack of tools to examine mechanisms and identify biomarkers in the dog. To address this issue, we developed an Affymetrix-based oligonucleotide microarray capable of monitoring the expression of thousands of canine genes in parallel. The custom canine array contains 22,774 probe sets, consisting of 13,729 canine and 9045 human-derived probe sets. To improve cross-species hybridization with human-derived probes, the detection region was moved from the variable 3' UTR to the more homologous coding region. Testing of this strategy was accomplished by comparing hybridization of naive dog liver RNA to the canine array (coding region design) and human U133A array (standard 3' design). Although raw signal intensity was greater with canine-specific probe sets, human-derived probes detected the expression of additional liver transcripts. To assess the ability of this tool to detect differential gene expression, the acute phase response was examined in beagle dogs given lipopolysaccharide (LPS). Hepatic gene expression 4 and 24 h post-LPS administration was compared to gene expression profiles of vehicle-treated dogs (n = 3/group). Array data was consistent with an acute inflammatory response, with transcripts for multiple cytokines and acute phase proteins markedly induced 4 h after LPS challenge. Robust changes in the expression of transcripts involved with glucose homeostasis, biotransformation, and extracellular matrix remodeling were observed 24 h post-dose. In addition, the canine array identified several potential biomarkers of hepatic inflammation. Strong correlations were found between gene expression data and alterations in clinical chemistry parameters such as serum amyloid A (SAA), albumin, and alkaline phosphatase (ALP). In summary, this new genomic tool successfully detected basal canine gene expression and identified novel aspects of the acute phase response in dog that shed new light on mechanisms underlying inflammatory processes.
Descriptors: immune system, chemical coordination and homeostasis, molecular genetics, biochemistry and molecular biophysics, toxicology, affymetrix based oligonucleotide microarray, genetic techniques, laboratory techniques, canine microarray, gene expression analysis, acute phase response, biotransformation, canine genomics, extracellular matrix remodeling, glucose homeostasis, hepatic gene expression, inflammation, toxicogenomics .

Horwitz, M., K.F. Benson, Z. Duan, F.Q. Li, and R.E. Person (2004). **Hereditary neutropenia: dogs explain human neutrophil elastase mutations**. *Trends in Molecular Medicine* 10(4): 163-170 ISSN: 1471-4914.
NAL Call Number: QH506
Abstract: Mutations in ELA2 the gene encoding neutrophil elastase (NE), cause the human diseases cyclic neutropenia (CN) and severe congenital neutropenia (SCN). Numerous mutations are known, but their lack of consistent biochemical effect has proven puzzling. The

recent finding that mutation of AP3B1, which encodes the P subunit of adaptor protein complex 3 (AP3), is the cause of canine CN suggests a model for the molecular basis of hereditary neutropenias, involving the mistrafficking of NE: AP3 recognizes NE as a cargo protein, and their interaction implies that NE is a transmembrane protein. Computerized algorithms predict two NE transmembrane domains. Most CN mutations fall within predicted transmembrane domains and lead to excessive deposition of NE in granules, whereas SCN mutations usually disrupt the AP3 recognition sequence, resulting in excessive transport to the plasma membrane.
Descriptors: molecular genetics, biochemistry and molecular biophysics, cyclic neutropenia, blood and lymphatic disease, genetics, hereditary neutropenia, blood and lymphatic disease, genetic disease, immune system disease, severe congenital neutropenia, computerized algorithm, mathematical and computer techniques, gene product interactions.

Hunter, L.S., D.J. Sidjanin, G.M. Acland, M. Villagrasa, and G.D. Aguirre (2003). **Evaluation of pax6 for mutations causing inherited ocular diseases in canine models**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*
Abstract: Purpose: Normal ocular development is dependent on the transcription factor PAX6. Mutations in PAX6 can result in aniridia, cataract, glaucoma, foveal hypoplasia and optic nerve hypoplasia in man. In mice, mutations in Pax6 cause the Small Eyepheonotype characterized by microphthalmia, abnormal lens and iris development and cataract. The purpose of this study is to evaluate the canine PAX6 gene for mutations causal to inherited ocular disease in canine models. Methods: Nine breeds of dog were identified having inherited forms of ocular disease for which PAX6 is a candidate gene. Two affected dogs from each breed were evaluated and their PAX6 sequence compared to canine wildtype sequence. Genomic DNA was prepared from whole blood and exons were scanned using intronic primers. Since the sequence for intron 4 could not be amplified, exon 4 was sequenced using primers in intron 3 and at the 3' end of exon 4, and exon 5 was sequenced using primers at the 5' end of exon 5 and in intron 5. Similarly, because of a homopolymer in the 3'UTR, exon 13 was evaluated using primers in intron 12 and at the 3' end of exon 13. Results: Thirteen exons plus an alternatively spliced exon (5a) are being examined in nine dog breeds with inherited eye diseases including cataracts, microphthalmia, persistent pupillary membranes, rod-cone dysplasia 2, cone-rod dystrophy 1 and 2, and aniridia. To date, no mutations associated with disease have been identified in the exons so far examined including the non-coding exons 1, 2, and 3. In addition to a previously identified SNP in intron 8, a single nucleotide change was identified in exon 7. This was a Cytosine -> Thymine change which did not result in an amino acid change. Microsatellites have been identified in exons 1 and 2, and in introns 6 and 7 which may facilitate linkage analysis. Conclusions: PAX6 plays an integral role in ocular development and mutations in this transcription factor cause different disease phenotypes. Evaluating canine models may identify novel disease phenotypes associated with PAX6 mutations.
Descriptors: molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, aniridia, congenital disease, eye disease, genetics, cataract, cone rod dystrophy 1, cone rod dystrophy 2, inherited ocular disease, genetic disease, genetics,

microphthalmia, persistent pupillary membrane, linkage analysis, genetic techniques, laboratory techniques, disease phenotype, ocular development.

Juraschko, K., A. Meyer Lindenberg, I. Nolte, and O. Distl (2003). **Analysis of systematic effects on congenital sensorineural deafness in german dalmatian dogs.** *Veterinary Journal* 166(2): 164-169. ISSN: 1090-0233.

NAL Call Number: SF601.V484

Abstract: We have analysed the systematic influences, phenotypic colour markers and the additive genetic variation for congenital sensorineural deafness (CSD) in German Dalmatian dogs in order to help elucidate the importance of phenotypic breed characteristics for genetic differences of CSD. Linear animal models using restricted maximum likelihood methods were employed to estimate variance components. Data were obtained from all three German Dalmatian kennel clubs associated with the German Association for Dog Breeding and Husbandry (VDH). CSD was recorded by standardized protocols for brainstem auditory-evoked response (BAER). The material included 1899 German Dalmatian dogs from 354 litters in 169 different kennels. BAER testing results were from the years 1986 to 1999. Pedigree information was available for up to seven generations. The animal model regarded the fixed effects of sex, coat colour, eye colour, presence of patches, litter size, percentage of examined puppies per litter, kennel club, and inbreeding coefficient. The common environment of the litter and kennel as well as the additive genetic effect of the animal were taken into account as randomly distributed effects. The fixed effects of eye colour, percentage of puppies examined per litter and kennel club were significant in the mixed model analysis. A significant proportion of additive genetic variation could be shown despite corrections for phenotypic colour variants. The heritability estimate for CSD in German Dalmatian dogs was h2 = 0.27 +- 0.07. The additive genetic correlation of CSD with presence of blue eyes was rg = 0.53 +- 0.41 and with presence of patches rg = -0.36 +- 0.24. We concluded that additional genes other than those associated with phenotypic colour markers in German Dalmatian dogs significantly contribute to the occurrence of CSD.

Descriptors: molecular genetics, biochemistry and molecular biophysics, nervous system, neural coordination, sense organs, sensory reception, veterinary medicine, medical sciences, congenital sensorineural deafness, CSD, congenital disease, ear disease, nervous system disease, diagnosis, genetics, therapy, german association for dog breeding and animal husbandry, brainstem auditory evoked response, breeding, genetic variation, phenotypic color markers.

Konety, B.-R., T.-S. Griffith, S.-J. Sirintrapun, J.-M. Rippentrop, A.-H. Stolpen, B.-R. De-Young, T.-L. Ratliff, and R.-D. Williams (2003). **Effect of intra-prostatic injection of adenovirus-trail in vivo in the dog prostate.** *Journal of Urology* 169(4 Supplement): 212. ISSN: 0022-5347.

NAL Call Number: 448.8 J8234

Descriptors: methods and techniques, molecular genetics, biochemistry and molecular biophysics, reproductive system, reproduction , h and e staining, hematoxylin eosin staining, histology and cytology techniques, laboratory techniques, intra prostatic injection, clinical techniques, pelvic computed tomography, imaging and microscopy techniques, radical prostatectomy, therapeutic and prophylactic techniques, periprostatic inflammation.

Schneider, M.R., H. Adler, J. Braun, B. Kienzle, E. Wolf, and H.J. Kolb (2007). **Canine embryo-derived stem cells--toward clinically relevant animal models for evaluating efficacy and safety of cell therapies.** *Stem Cells Dayton, Ohio* 25(7): 1850-1. ISSN: 1066-5099.
Descriptors: embryo, mammalian cytology, embryonic stem cells cytology, models, animal, tissue therapy adverse effects, antigens, cd34 genetics, antigens, cd34 metabolism, cell differentiation, cell separation, dogs, gata2 transcription factor genetics, gata2 transcription factor metabolism, gene expression regulation, rna, messenger genetics, rna, messenger metabolism, treatment outcome.

Shelton, G.D., M. Podell, L. Poncelet, S. Schatzberg, E. Patterson, H.C. Powell, and A.P. Mizisin (2003). **Inherited polyneuropathy in leonberger dogs: a mixed or intermediate form of charcot-marie-tooth disease?** *Muscle and Nerve* 27(4): 471-477. ISSN: 0148-639X.
Abstract: A spontaneous distal, symmetrical polyneuropathy in related Leonberger dogs with onset between 1 to 9 years of age was characterized clinically, electrophysiologically, histologically, and morphometrically. Exercise intolerance and weakness was associated with a high-steppage pelvic-limb gait, a loss or change in the pitch of the bark, and dyspnea. Neurological examination revealed marked atrophy of the distal limb muscles, depressed spinal and cranial nerve reflexes, and weak or absent movement of the laryngeal and pharyngeal muscles. Electrophysiological evaluation was consistent with denervation and was characterized by loss or marked attenuation of compound muscle action potentials and slowed motor nerve conduction velocity. Muscle biopsy specimens showed neurogenic atrophy. Chronic nerve fiber loss associated with decreased myelinated fiber density and a shift of the axonal size-frequency distribution toward smaller fibers was the predominant finding in peripheral nerve specimens. Pedigree analysis of a large multigenerational family, including nine sibships with at least one affected individual, suggested X-linked inheritance. Mutational and linkage analysis of this family may aid in identification of the chromosomal loci and gene responsible for this inherited axonal neuropathy. Further characterization of this inherited axonal neuropathy may establish the Leonberger dog as a spontaneous animal model of inherited axonal neuropathy and possibly lead to the discovery of a new gene or genes associated with axonal variants.
Descriptors: molecular genetics, biochemistry and molecular biophysics, nervous system, neural coordination, Charcot Marie tooth disease, congenital disease, genetic disease, muscle disease, nervous system disease, chronic nerve fiber loss, distal limb muscle atrophy, dyspnea, respiratory system disease, exercise intolerance, inherited polyneuropathy, genetic disease, muscle weakness, neurogenic atrophy, cranial nerve reflex, motor nerve conduction velocity, myelinated fiber density, spinal nerve reflex.

Shin, D. and C. Park (2004). **N-terminal extension of canine glutamine synthetase created by splicing alters its enzymatic property.** *Journal of Biological Chemistry* 279(2): 1184-1190. ISSN: 0021-9258.
NAL Call Number: 381 J824
Abstract: It was found that an extra exon exists in the first intron of glutamine synthetase gene, generated by means of alternative splicing (Shin, D., Park, S., and Park, C. (2003) Biochem. J. 374, 175-184). Inclusion of this exon decreased the translation of glutamine synthetase (GS) in human, dog, and mouse. When translated in vitro with the canine GS

transcript containing the exon, we obtained two different species of GS enzymes. Besides the known 45-kDa protein, the extended form of GS was identified with additional 40 amino acids on its N-terminal end. An upstream ATG in the extra exon served as a translation initiator for the long form of GS. When the long transcript was translated in vivo in animal cells, only the long GS was expressed. On the other hand, the long GS is less predominant relative to the short one in canine tissues including brain and liver. Subcellular fractionation of canine brain revealed that the long GS is present in all cellular compartments as is the short one, which is consistent with fluorescence microscopy data obtained with green fluorescent protein fused to GS. The short (SGS) and long (LGS) forms of canine GS were purified in Escherichia coli and shown to have similar Km values for L-glutamate and hydroxylamine. However, the Km values for ATP were slightly altered, 1.3 and 1.9 mM for the short and long GSs, respectively. The Kis for L-methionine-S-sulfoximine (MSOX), a highly potent ATP-dependent inactivator of GS, were considerably different such that the values are 0.067 and 0.124 mM for the short and long forms, respectively. When the intrinsic fluorescences of tryptophans were monitored upon bindings of chloride and metal ions without any effect on the oligomeric state, the pattern of quenching in LGS was significantly different from that of SGS. Taken together, the N-terminal extension in the long isoform of GS induces a conformational change of core enzyme, leading to a change in affinity to its substrates as well as in the effector-induced conformational alterations.
Descriptors: enzymology, biochemistry and molecular biophysics, genetics, metabolism .

Shin, D., S. Park, and C. Park (2003). **A splice variant acquiring an extra transcript leader region decreases the translation of glutamine synthetase gene.** *Biochemical Journal* 374(1): 175-184. ISSN: 0264-6021.
NAL Call Number: QP501.B64
Abstract: The expression of glutamine synthetase (GS), catalysing the ATP-dependent conversion of glutamate and ammonia into glutamine, is transcriptionally and post-transcriptionally regulated. The genomic structure of dog GS shown in the present study is basically similar to that of other mammals in that it is composed of seven exons and six introns. Using 5'-cRACE (where cRACE stands for circular rapid amplification of cDNA ends) and reverse transcriptase-PCR, we identified an additional exon (120 bp) in the first intron, designated in the present study as exon 1'. By means of alternative splicing, the GS gene produces an altered form of GS transcript with 5'-untranslated region (UTR) containing the exon 1'. This alternative transcript is abundantly expressed in brain, whereas it is found at lower levels in other tissues. In the human and mouse GS genes, extra exons are also found at the corresponding site of the intron 1 but with different sizes. An exon-trapping experiment for the GS gene in COS-7, Madin-Darby canine kidney and SK-N-SH cells revealed that the pattern of alternative splicing is variable in different cell types. The propensity of forming a secondary structure is predicted to be considerably higher in the presence of extra 5'-UTR, suggesting the possibility of a translational effect. To test this, we performed a reporter assay for fusions with different 5'-UTRs, demonstrating that the long form with extra 5'-UTR was translated 20- and 10-fold less than the short one in SK-N-SH and Neuro-2A cells respectively. Similarly, translations of human and mouse transcripts with extra 5'-UTRs were less efficient, showing 6-8-fold reductions in SK-N-SH cells. Furthermore, when we mutated an ATG sequence contained in the exon 1', the suppression of translation was partially relieved,

suggesting that the negative regulation by an extra 5'-UTR is, to some extent, due to an abortive translation from the upstream ATG.
Descriptors: molecular genetics, biochemistry and molecular biophysics, 5' circular rapid amplification of cdna ends, 5' crace, genetic techniques, laboratory techniques, reverse transcriptase pcr, rt pcr, genetic techniques, laboratory techniques, alternative splicing, gene expression.

Vassilopoulos, G. and A. Rethwilm (2008). **The usefulness of a perfect parasite.** *Gene Therapy* 15(19): 1299-1301.
Descriptors: gene therapy methods, leukocyte adhesion deficiency syndrome therapy, dogs, genetic vectors administration and dosage, genetic vectors genetics, models, animal, spumavirus genetics, transduction, genetic methods.

Yuasa, K., M. Yoshimura, N. Urasawa, S. Ohshima, J.M. Howell, A. Nakamura, T. Hijikata, Y. Miyagoe Suzuki, and S. Takeda (2007). **Injection of a recombinant AAV serotype 2 into canine skeletal muscles evokes strong immune responses against transgene products.** *Gene Therapy* 14(17): 1249-60. ISSN: 0969-7128.
Abstract: Using murine models, we have previously demonstrated that recombinant adeno-associated virus (rAAV)-mediated microdystrophin gene transfer is a promising approach to treatment of Duchenne muscular dystrophy (DMD). To examine further therapeutic effects and the safety issue of rAAV-mediated microdystrophin gene transfer using larger animal models, such as dystrophic dog models, we first investigated transduction efficiency of rAAV in wild-type canine muscle cells, and found that rAAV2 encoding beta-galactosidase effectively transduces canine primary myotubes in vitro. Subsequent rAAV2 transfer into skeletal muscles of normal dogs, however, resulted in low and transient expression of beta-galactosidase together with intense cellular infiltrations in vivo, where cellular and humoral immune responses were remarkably activated. In contrast, rAAV2 expressing no transgene elicited no cellular infiltrations. Co-administration of immunosuppressants, cyclosporine and mycophenolate mofetil could partially improve rAAV2 transduction. Collectively, these results suggest that immune responses against the transgene product caused cellular infiltration and eliminated transduced myofibers in dogs. Furthermore, in vitro interferon-gamma release assay showed that canine splenocytes respond to immunogens or mitogens more susceptibly than murine ones. Our results emphasize the importance to scrutinize the immune responses to AAV vectors in larger animal models before applying rAAV-mediated gene therapy to DMD patients.
Descriptors: dependovirus genetics, gene therapy adverse effects, genetic vectors adverse effects, muscle, skeletal immunology, muscular dystrophy, animal therapy, muscular dystrophy, duchenne therapy, base sequence, calmodulin genetics, cyclosporine administration and dosage, dogs, dystrophin genetics, dystrophin metabolism, gene therapy methods, genetic engineering, genetic vectors genetics, immunosuppressive agents administration and dosage, injections, intramuscular, interferon gamma immunology, lymphocyte activation, mice, mice, inbred c57bl, models, animal, molecular sequence data, muscle fibers, skeletal immunology, muscle fibers, skeletal virology, muscular dystrophy, animal immunology, muscular dystrophy, duchenne immunology, parvoviridae infections immunology, rna, messenger analysis, reverse transcriptase polymerase chain reaction, species specificity, t lymphocytes,

cytotoxic immunology, transduction, genetic methods, transgenes, beta galactosidase genetics.

Musculoskeletal System

Allen, M.R. and D.B. Burr (2008). **Changes in vertebral strength-density and energy absorption-density relationships following bisphosphonate treatment in beagle dogs.** *Osteoporosis International* 19(1): 95-9. ISSN: 0937-941X.

NAL Call Number: RC931.O8

Abstract: We aimed to determine the effects of bisphosphonates on mechanical properties independent of changes in bone density. Our results show that at equivalent bone densities, vertebrae from beagles treated with bisphosphonate have equivalent bone strength and reduced bone energy absorption compared to those from untreated animals. INTRODUCTION: Assessing the relationship between mechanical properties and bone density allows a biomechanical evaluation of bone quality, with differences at a given density indicative of altered quality. The purpose of this study was to evaluate the strength-density and energy absorption-density relationships in vertebral bone following a one-year treatment with clinical doses of two different bisphosphonates in beagle dogs. METHODS: Areal bone mineral density (aBMD) and compressive mechanical properties (ultimate load and energy absorption) were assessed on lumbar vertebrae from skeletally mature beagle dogs treated with vehicle (VEH), alendronate (ALN), or risedronate (RIS). Relationships among properties were assessed using analyses of covariance. RESULTS: Neither treatment altered the strength-density relationship compared to VEH, suggesting increases in vertebral strength with bisphosphonate-treatment are explained by increased density. The energy absorption-density relationship was altered by ALN, resulting in significantly lower energy absorption capacity at a given aBMD compared to both VEH (-22%) and RIS (-14%). CONCLUSIONS: These data document that after adjusting for increased aBMD, vertebrae from animals treated with bisphosphonates have similar strength as those from untreated animals. Conversely, when adjusted for increased aBMD, alendronate treatment, but not risedronate treatment, significantly reduces the energy required for vertebral fracture, indicative of an alteration in bone quality.

Descriptors: bone density drug effects, bone density conservation agents pharmacology, diphosphonates pharmacology, lumbar vertebrae drug effects, alendronate pharmacology, compressive strength, dogs, etidronic acid analogs and derivatives, etidronic acid pharmacology, models, animal.

Arican, M., M. Ortatatli, K. Yigitarslan, and C. Ceylan (2003). **Osteogenic ability of free perichondreal autografts in canine tibial defects: an experimental study.** *Journal of Experimental Animal Science* 42(4): 203-217. ISSN: 0939-8600.

NAL Call Number: QL1.J687

Abstract: This study set out to establish the effect of transplanting perichondreum on bone healing at sites of tibial bone defects in an experimental dog model. Transplantation of free, autologous, non-vascularised, perichondreal grafts to the distal of right anteromedial plane side of the tibia was compared with non-transplantation on the proximal side of the same bone. In experimental dogs (n=7), a 5 cm piece segment of perichondreum, that has been

excised from the thirteenth rib of the same animal, was transplanted to the midddle defect fracture site of bone, but not to the control proximal defect fracture site. The dogs were allowed to recover from the operation and were kept 21 days in cages, with free-range. On days 30 (Group I) and 45 (Group II) after operations, the dogs were euthanatized. Histopathologically, defects in 30 days treated perichondreum group were filled by new ossified tissue while control defects in the same period were not fully resurfaced. The new ossified tissue consisted of a thin and inadequate trabeculae. In 45 days treated groups, defects with transplanting perichondreum were filled by thick trabeculae converting into a compact bone tissue. The control defects of this group, however, were filled by an extreme callus overflowing to medulla and bone surface. This study has provided evidence to show that autologous, non-vascularized perichondreum retains an osteogenic ability when transplanted to tibial bone defect sites. It appears that callus formation occurred within the perichondreum grafting which resembles that of enchondral and intramembranous ossification.
Descriptors: methods and techniques, skeletal system, movement and support, tibial bone defects, bone disease, perichondrial autograft, experimental surgical techniques, laboratory techniques, ossification .

Beebe, K.S., J. Benevenia, B.E. Tuy, C.A. DePaula, R.D. Harten, and W.F. Enneking (2009). **Effects of a new allograft processing procedure on graft healing in a canine model: a preliminary study.** *Clinical Orthopaedics and Related Research* 467(1): 273-80.
Abstract: Graft healing in vivo can be affected by allograft processing. We asked whether a new processing technique influenced graft-host healing compared with autograft and a standard processing technique in a canine ulna model. We used bilateral intercalary allografts or autografts in the ulna of 13 skeletally mature male coonhounds. Each animal received two allografts, either one autograft and one allograft, or two autografts. At term (90 days), the graft sites were harvested. We assessed union with high-resolution xray imaging. Each specimen was processed for nondecalcified histologic analysis to assess the graft-host interface. Quantitative histomorphometric analysis was performed to determine spatial location and area of bone. Radiographic analysis, histologic analysis, and histomorphometric measures revealed no differences in union, mean total bone area, or total endosteal/intramedullary bone for the new process, standard process, and autografts. Our preliminary data suggest the new processing techniques may increase the safety of allograft transplantation without adversely affecting union when compared with standard processing techniques and autograft in a canine model.
Descriptors: bone transplantation, fracture healing, tissue and organ harvesting methods, ulna fractures surgery, dogs, models, animal, pilot projects, transplantation, autologous, transplantation, homologous, ulna fractures pathology, ulna fractures radiography.

Brandt, K.D., G.N.J. Smith, and S.L. Myers (2004). **Hyaluronan injection affects neither osteoarthritis progression nor loading of the oa knee in dogs**. *Biorheology* 41(3-4): 493-502. ISSN: 0006-355X.
NAL Call Number: QH505.A1B5
Abstract: We previously reported that intraarticular injections of hyaluronan (HA), administered prophylactically to dogs in whom knee osteoarthritis had been induced by transection

of the anterior cruicate ligament, did not significantly modify the intraarticular pathology but decreased the proteogylcan concentration of the articular cartilage by as much as 30%. Because the cartilage proteoglycan concentration is directly related to the stiffness of the tissue, these results raised the possibility that intraarticular HA therapy could exacerbate OA. In the present study, using a different HA formulation, with a longer interval between intraarticular HA injection and examination of joint tissues, we found that neither prophylactic nor therapeutic administration of HA had an effect on the severity of OA pathology, the magnitude of vertical ground reaction forces generated by the unstable hind limb (a surrogate for joint pain), or the cartilage proteoglycan concentration. The data suggest that the suppression of proteoglycan synthesis induced by HA is temporary and fully reversible and that HA injections do not result in overloading of the OA extremity. A significant correlation was noted between the severity of chondropathy and the magnitude of the vertical ground reaction forces generated by the unstable limb.
Descriptors: animal care, pharmacology, skeletal system, movement and support, osteoarthritis, joint disease.

Candido, P.L. and B.J. Konig (2004). **Histological analysis of bone/heteroplastic implant interfaces in dog tibia.** *Annals of Anatomy* 186(1): 69-73. ISSN: 0940-9602.
Abstract: This work presents histological analysis of interfaces between bone and heteroplastic implants in dog tibias. The study was performed in four tibias (of four mongrel dogs) into which cylindrical implants were inserted. One ceramic (titania) implant and three grit-blasted titanium implants (with sandblasted and acid-corroded surfaces) were chosen for histological analysis of the implant surface/bone tissue interface. The implants remained in the tibias for eight months and none were loaded during this period. The animals were subsequently sacrificed and the samples were processed for analysis. Light microscope analysis revealed a large amount of osteoid tissue and proximity of osteoblasts and osteocytes to the implant surfaces. In addition, little or no fibrous tissue was observed between the bone and implant surfaces. The titanium implants presented better osseointegration than did the ceramic implant.
Descriptors: biomedical engineering, allied medical sciences, methods and techniques, orthopedics, human medicine, medical sciences, biotitatnium implant, prosthetic, bone, heteroplastic implant, prosthetic, ceramic titania implant, prosthetic, grit blasted titanium implant, prosthetic, histological analysis, histology and cytology techniques, laboratory techniques, light microscope analysis, imaging and microscopy techniques, subperiosteal implant, prosthetic .

Cerri, D.G., L.C. Rodrigues, S.R. Stowell, D.D. Araujo, M.C. Coelho, S.R. Oliveira, J.C. Bizario, R.D. Cummings, M. Dias Baruffi, and M.C. Costa (2008). **Degeneration of dystrophic or injured skeletal muscles induces high expression of Galectin-1.** *Glycobiology* 18(11): 842-50.
NAL Call Number: QP901.J6
Abstract: Muscle degenerative diseases such as Duchenne Muscular Dystrophy are incurable and treatment options are still restrained. Understanding the mechanisms and factors responsible for muscle degeneration and regeneration will facilitate the development of

novel therapeutics. Several recent studies have demonstrated that Galectin-1 (Gal-1), a carbohydrate-binding protein, induces myoblast differentiation and fusion in vitro, suggesting a potential role for this mammalian lectin in muscle regenerative processes in vivo. However, the expression and localization of Gal-1 in vivo during muscle injury and repair are unclear. We report the expression and localization of Gal-1 during degenerative-regenerative processes in vivo using two models of muscular dystrophy and muscle injury. Gal-1 expression increased significantly during muscle degeneration in the murine mdx and in the canine Golden Retriever Muscular Dystrophy animal models. Compulsory exercise of mdx mouse, which intensifies degeneration, also resulted in sustained Gal-1 levels. Furthermore, muscle injury of wild-type C57BL/6 mice, induced by BaCl(2) treatment, also resulted in a marked increase in Gal-1 levels. Increased Gal-1 levels appeared to localize both inside and outside the muscle fibers with significant extracellular Gal-1 colocalized with infiltrating CD45(+) leukocytes. By contrast, regenerating muscle tissue showed a marked decrease in Gal-1 to baseline levels. These results demonstrate significant regulation of Gal-1 expression in vivo and suggest a potential role for Gal-1 in muscle homeostasis and repair.
Descriptors: galectin 1 metabolism, muscle, skeletal injuries, muscle, skeletal metabolism, muscular dystrophy, animal metabolism, antigens, cd45 immunology, antigens, cd45 metabolism, dogs, fluorescent antibody technique, galectin 1 analysis, leukocytes metabolism, mice, mice, inbred c57bl, mice, inbred mdx, models, animal, muscular dystrophy, animal chemically induced, regeneration physiology.

Coleman, J.C., R.T. Hart, and D.B. Burr (2003). **Reconstructed bone end loads on the canine forelimb during gait.** *Journal of Biomechanics* 36(12): 1837-1844. ISSN: 0021-9290.
NAL Call Number: TA166.J6
Abstract: The objective of this work was to determine bone loading conditions that, when applied to a finite element model, would best reproduce the in vivo strain field as measured by surface-mounted strain rosettes. The present study adopts the basic mathematical approach to load reconstruction introduced by Weinans and Blankevoort (J. Biomech. 28 (1995) 739) who determined the relationship between applied loads and bone strain distribution using ex vivo calibration testing. Our method eliminates the need for subsequent ex vivo calibration tests by instead substituting a computational calibration procedure. This first application of the method is with in vivo strains on the canine forelimb during gait (Coleman et al., J. Biomech. 35 (2002) 1677), but with further refinements the method could be used to reconstruct the in vivo loading conditions in living subjects.
Descriptors: methods and techniques, models and simulations, computational biology, skeletal system, movement and support, finite element model, gait .

Cui, L., B. Liu, G. Liu, W. Zhang, L. Cen, J. Sun, S. Yin, W. Liu, and Y. Cao (2007). **Repair of cranial bone defects with adipose derived stem cells and coral scaffold in a canine model.** *Biomaterials* 28(36): 5477-86. ISSN: 0142-9612.
NAL Call Number: R857.M3B48
Abstract: Adipose derived stem cells (ASCs) with osteogenic differentiation potential have been documented as an alternative cell source for bone regeneration. However, most of previous in vivo studies were carried out on small animals along with relatively short-term

follow-up. In this study, we investigated the feasibility of using ASCs and coral scaffolds to repair a cranial bone defect in a canine model, and followed up the outcome for up to 6 month. Autologous ASCs isolated from canine subcutaneous fat were expanded, osteogenically induced, and seeded on coral scaffolds. Bilateral full-thickness defects (20 mm x 20 mm) of parietal bone were created. The defects were either repaired with ASC-coral constructs (experimental group) or with coral alone (control group). Three-dimensional CT scan showed that new bones were formed in the experimental group at 12 weeks post-implantation, while coral scaffolds were partially degraded in the control group. By radiographic analysis at 24 weeks post-transplantation, it was shown that an average of 84.19+/-6.45% of each defect volume had been repaired in experimental side, while the control side had only 25.04+/-18.82% of its volume filled. Histological examination revealed that the defect was repaired by typical bone tissue in experimental side, while only minimal bone formation with fibrous connection was observed in the control group. The successful repair of critical-sized bone defects via the current approach substantiates the potentiality of using ASCs with coral scaffolds for bone regeneration.

Descriptors: adipocytes cytology, craniofacial abnormalities pathology, craniofacial abnormalities surgery, skull abnormalities, skull cytology, stem cell transplantation methods, stem cells cytology, cell differentiation, cell separation, craniofacial abnormalities ultrastructure, dogs, microscopy, electron, scanning, models, animal, tomography, x ray computed.

d'Anjou, M.A., E. Troncy, M. Moreau, F. Abram, J.P. Raynauld, J. Martel Pelletier, and J.P. Pelletier (2008). **Temporal assessment of bone marrow lesions on magnetic resonance imaging in a canine model of knee osteoarthritis: impact of sequence selection.** *Osteoarthritis and Cartilage OARS, Osteoarthritis Research Society* 16(11): 1307-11.

NAL Call Number: RC931.O67

Abstract: OBJECTIVE: To assess the evolution of bone marrow lesions (BMLs) in a canine model of knee osteoarthritis (OA) using three different magnetic resonance imaging (MRI) sequences. DESIGN: Three MRI sequences [coronal, T1-weighted three-dimensional fast gradient recalled echo (T1-GRE), sagittal fat-suppressed 3D spoiled gradient echo at a steady state (SPGR), and sagittal T2-weighted fast spin echo with fat saturation (T2-FS)] were performed at baseline, and at week 4, 8 and 26 in five dogs following transection of the anterior cruciate ligament. The same reader scored (0-3) subchondral BMLs twice, in blinded conditions, according to their extent in nine joint subregions, for all imaging sessions, and independently on the three MRI sequences. Correlation coefficients and Bland-Altman plots evaluated intra-reader repeatability. Readings scores were averaged and the nine subregions were summed to generate global BML scores. RESULTS: BMLs were most prevalent in the central and medial portions of the tibial plateau. Intra-reader repeatability was good to excellent for each sequence (r(s)=0.87-0.97; P<0.001). Maximal intra-reader variability (24%) was reached on T2-FS and was associated to higher scores (P<0.05). Global BML scores increased similarly on all three sequences until week 8 (P<0.05). At week 26, score on T2-FS was decreased, being lower when compared to T1-GRE and SPGR (P<0.05). CONCLUSION: In this canine OA model, the extent of BMLs varies in time on different MRI sequences. Until the complex nature of these lesions is fully resolved, it is suggested that to accurately assess the size and extent of BMLs, a combination of different sequences should be used.

Descriptors: bone marrow pathology, bone marrow diseases pathology, knee joint pathology, magnetic resonance imaging methods, osteoarthritis, knee pathology, dogs, models, animal.

Decramer M , Reid M B , and De Troyer A (1985). **Relationship between parasternal intercostal length and rib cage displacement in dogs**. *Journal of Applied Physiology* 58(5): 1517-1520. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: The relationship between parasternal intercostal length and rib cage cross-sectional area was examined in 9 supine dogs during passive inflation and during quiet breathing before and after phrenicotomy. Parasternal intercostal length (PSL) was measured with a sonomicrometry technique and rib cage cross-sectional area (Arc) was measured with a Respitrace coil placed around the middle rib cage. During active inspiration as well as during passive inflation, PSL decreased as Arc increased. However, the relationship between PSL and Arc during active inspiration, whether in the intact or phrenicotomized animal, was almost invariably different from that during passive inflation, so that the same increase in Arc was associated with a greater decrease in PSL in the former than in the latter instance. This difference between passive inflation and active inspiration was probably due to the active contraction of the parasternals during inspiration and the consequent caudal displacement of the sternum. In upright humans, the sternum moved cephalad and not caudad during inspiration, so the relationship between PSL and Arc during active breathing might be similar to that during passive inflation.
Descriptors: muscular system, movement and support, nervous system, neural coordination, respiratory system, respiration, surgery, medical sciences, respiratory muscle passive inflation active inspiration.

Derwin, K.A., M.J. Codsi, R.A. Milks, A.R. Baker, J.A. McCarron, and J.P. Iannotti (2009). **Rotator Cuff Repair Augmentation in a Canine Model with Use of a Woven Poly-L-Lactide Device**. *The Journal of Bone and Joint Surgery* 91: 1159-1171. ISSN: 1535-1386.
Abstract: Despite advances in surgical treatment options, failure rates of rotator cuff repair have continued to range from 20% to 90%. Hence, there is a need for new repair strategies that provide effective mechanical reinforcement of rotator cuff repair as well as stimulate and enhance the intrinsic healing potential of the patient. The purpose of this study was to evaluate the extent to which augmentation of acute repair of rotator cuff tendons with a newly designed poly-L-lactide repair device would improve functional and biomechanical outcomes in a canine model. METHODS: Eight adult, male mongrel dogs (25 to 30 kg) underwent bilateral shoulder surgery. One shoulder underwent tendon release and repair only, and the other was subjected to release and repair followed by augmentation with the repair device. At twelve weeks, tendon retraction, cross-sectional area, stiffness, and ultimate load of the repair site were measured. Augmented repairs underwent histologic assessment of biocompatibility. In addition, eight pairs of canine cadaver shoulders underwent infraspinatus injury and repair with and without device augmentation with use of identical surgical procedures and served as time-zero biomechanical controls. Eight unpaired, canine cadaver shoulders were included as normal biomechanical controls. RESULTS: At time zero, repair augmentation significantly increased the ultimate load (23%) ($p = 0.034$) but not the stiffness of the canine infraspinatus tendon repair. At twelve weeks, the poly-L-lactide scaffold was observed

to be histologically biocompatible, and augmented repairs demonstrated significantly less tendon retraction (p = 0.008) and significantly greater cross-sectional area (137%), stiffness (26%), and ultimate load (35%) than did repairs that had not been augmented (p < 0.001, p = 0.002, and p = 0.009, respectively). CONCLUSIONS: While limiting but not eliminating tendon repair retraction, the augmentation device provided a tendon-bone bridge and scaffold for host tissue deposition and ingrowth, resulting in improved biomechanical function of the repair at twelve weeks.

Descriptors: male mongrel dogs, bilateral shoulder surgery, canine cadaver shoulders, tendon release, tendon retraction, stiffness, poly-L-lactide scaffold, repair

Di Pasquale, D.J., M. Bhandari, A. Tov, and E.H. Schemitsch (2007). **The effect of high and low pressure pulsatile lavage on soft tissue and cortical blood flow: a canine segmental humerus fracture model.** *Archives of Orthopaedic and Trauma Surgery* 127(10): 879-84. ISSN: 0936-8051.

NAL Call Number: RD731

Abstract: OBJECTIVE: To determine the effect of high pressure pulsatile lavage (HPPL) and low pressure pulsatile lavage (LPPL) on cortical and soft tissue blood flow in a canine humerus segmental fracture model. DESIGN: Midshaft humeral osteotomies to create a 2-cm segment of diaphyseal bone were performed on bilateral canine humeri. Each osteotomy site was irrigated using either high pressure (n = 6) or low pressure (n = 5) pulsatile lavage prior to stabilization with a 5-mm steinman pin. Perfusion of cortical bone, periosteum, and biceps muscle was measured using Laser Doppler Flowmetry during four intraoperative intervals: pre-osteotomy, post-osteotomy, post-lavage, and post-nailing. RESULTS: Following osteotomy, a significant drop occurred in cortical perfusion (HPPL P = 0.049, LPPL P = 0.021) and in periosteal flow (HPPL P = 0.019, LPPL P = 0.012). Following irrigation there was no significant decrease in blood flow in either group for muscle (HPPL P = 0.249, LPPL P = 0.41), periosteum (HPPL P = 0.381, LPPL P = 0.402), or cortex (HPPL P = 0.398, LPPL P = 0.352) measurements. There was no significant difference between irrigation groups in post-lavage perfusion values for muscle (P = 0.326), periosteum (P = 0.452), and cortex (P = 0.464). Cortical perfusion decreased significantly post-nailing (HPPL P = 0.027, LPPL P = 0.047). Measurements did not differ significantly between groups at any other time interval. CONCLUSION: Although previous work has demonstrated an association between HPPL and detrimental structural changes in bone, this study demonstrates that HPPL does not adversely affect cortical or soft tissue blood flow acutely. Further, LPPL offers no acute benefit to cortical or soft tissue perfusion.

Descriptors: humeral fractures surgery, humerus blood supply, irrigation methods, muscle, skeletal blood supply, periosteum blood supply, dogs, fracture fixation, intramedullary, humerus surgery, laser doppler flowmetry, models, animal, osteotomy, pressure, regional blood flow.

Dubowitz, V. (2004). **Current and future therapy in muscular dystrophy; need for a common language between basic scientists and clinicians.** *Acta Myologica* 23(2): V-IX. ISSN: 1128-2460.

Abstract: This paper reviews the current therapy of Duchenne dystrophy, with the only two effective means of prolonging ambulation being the provision of knee-ankle-foot orthoses,

and administration of corticosteroids, and the prospects, for the future application in Duchenne dystrophy, of ongoing research in cell therapy, gene therapy, protein upregulation and pharmacological possibilities. A critical review is also provided on the inappropriate nomenclature currently used and the need for a common language between basic and clinical scientists. Amongst the major problems are equating the mdx mouse, with its mild clinical phenotype, and Duchenne dystrophy, with its clearly defined severe clinical phenotype; the use of inappropriate and often emotive terminology to describe the pathological changes, such as "rescue", "reversal", "prevention", in place of describing the actual changes in acceptable descriptive language; and the use of the term therapy, in place of experiments, both in the basic laboratory studies and also the clinical experiments of injection of cells or gene constructs into single small muscles. A missing link in the multidisciplinary efforts, in this field, is the almost total absence of mouse doctors, who can define, at a clinical level, the motor, respiratory and cardiac deficits in the dystrophic animal, and bridge the gap between the mouse scientists doing experimental studies in the laboratory and the clinicians and veterinarians involved in the care of humans and dogs with these disorders and speaking the same language in relation to the clinical aspects and the pathology.
Descriptors: Duchenne dystrophy, corticosteroid administration, cell therapy, gene therapy, experimental studies, clinical practice, human.

Eisenschenk, A., C. Witzel, M. Lautenbach, A. Ekkernkamp, U. Weber, and M.V. Kuntscher (2007). **Does chemotherapy impair the bone healing and biomechanical stability of vascularized rib and fibula grafts?** *Journal of Reconstructive Microsurgery* 23(1): 35-40. ISSN: 0743-684X.
Abstract: The purpose of this study was to observe the impact of chemotherapy on the healing and biomechanical properties of vascularized bone grafts. Ten male beagle dogs were divided into two experimental groups: a chemotherapy group (CH) and control group (C). Group CH received adjuvant and neo-adjuvant chemotherapy. Each animal of both groups underwent the following operative procedures. The 5th and 7th rib were removed and replaced by vascularized pedicle transfers of the adjacent 4th and 8th rib. Additionally, a free fibular flap was elevated and retransferred to the same anatomic position. The rate of bony union on plain x-ray was 100 percent in group C, 30 percent in the vascularized rib, and 80 percent in the fibula grafts of group CH. Microangiography demonstrated no avascular bone segments in group C and in the fibula flaps of group CH. The vascularized ribs of group CH presented with 20 percent avascular bone segments. Biomechanical tests focusing on the durability of the vascularized grafts against bending and torsion forces demonstrated a reduction of the average maximum bending times by 17 percent and 23.9 percent compared to the controls ($P < 0.05$). The twisting times were reduced by 13.8 percent (n.s.) and 32.5 percent ($P < 0.05$). The data demonstrated a clear worsening in bone healing and stability after simulated adjuvant and neo-adjuvant chemotherapy. Thus, a large animal model was established for the further determination of the effects of chemotherapy on different vascularized bone transfers.
Descriptors: antineoplastic agents pharmacology, bone transplantation pathology, bone and bones drug effects, angiography, antibiotics, antineoplastic pharmacology, antimetabolites, antineoplastic pharmacology, biomechanics, chemotherapy, adjuvant, dogs, doxorubicin pharmacology, fibula, methotrexate pharmacology, microradiography, models, animal, neo-adjuvant therapy, pliability, ribs, torque, wound healing drug effects.

Eswaran, S.K., M.R. Allen, D.B. Burr, and T.M. Keaveny (2007). **A computational assessment of the independent contribution of changes in canine trabecular bone volume fraction and microarchitecture to increased bone strength with suppression of bone turnover.** *Journal of Biomechanics* 40(15): 3424-31. ISSN: 0021-9290.
NAL Call Number: TA166.J6
Abstract: This study addressed the effects of changes in trabecular microarchitecture induced by suppressed bone turnover-including changes to the remodeling space-on the trabecular bone strength-volume fraction characteristics independent of changes in tissue material properties. Twenty female beagle dogs, aged 1-2 years, were treated daily with either oral saline (n=10 control) or high doses of oral risedronate (0.5mg/kg/day, n=10 suppressed) for a period of 1 year, the latter designed (and confirmed) to substantially suppress bone turnover. High-resolution micro-CT-based finite element models (18-mum voxel size) of canine trabecular bone cores (n=2 per vertebral body) extracted from the T-10 vertebrae were analyzed in both compressive and torsional loading cases. The same tissue-level material properties were used in all models, thus providing measures of tissue-normalized strength due only to changes in the microarchitecture. Suppressed bone turnover resulted in more plate-like architecture with a thicker and more dense trabecular structure, but the relationship between the microarchitectural parameters and volume fraction was unaltered ($p>0.05$). Though the suppressed group had a greater tissue-normalized strength as compared to the control group ($p<0.001$) for both compressive and torsional loading, the relationship between tissue-normalized strength and volume fraction was not significantly altered for compression ($p>0.13$) or torsion ($p>0.09$). In this high-density, non-osteoporotic animal model, the increases in tissue-normalized strength seen with suppression of bone turnover were entirely commensurate with increases in bone volume fraction and thus, no evidence of microarchitecture-related or "stress-riser" effects which may disproportionately affect strength were found.
Descriptors: bone density physiology, bone and bones cytology, bone and bones metabolism, computer simulation, dogs, finite element analysis, models, animal, stress, mechanical, tomography, x ray computed.

Flores Gasca, E., L. Rodriguez Fragoso, G.G. Farina, and J.R. Esparza (2003). **Evaluation of the healing and integration of demineralized bone using an allograft in plate in osteotomies in dogs.** *FASEB Journal* 17(4-5): A565. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: skeletal system, animal model, segmental bone defect, tibia, osteotomy, angiogenesis, osteoblast activity, laboratory techniques, therapeutic and prophylactic techniques

Frost Christensen, L.N., S.C. Mastbergen, M.E. Vianen, A. Hartog, J. DeGroot, G. Voorhout, A.M. van Wees, F.P. Lafeber, and H.A. Hazewinkel (2008). **Degeneration, inflammation, regeneration, and pain/disability in dogs following destabilization or articular cartilage grooving of the stifle joint.** *Osteoarthritis and Cartilage OARS, Osteoarthritis Research Society* 16(11): 1327-35.
Abstract: OBJECTIVE: The most used model for joint instability is the canine anterior cruciate ligament transection (ACLT)-model. The ACLT-model can be extended with a medial meniscectomy (MX) (i.e., ACLT-MX-model) to avoid unintentional, and with that variable, meniscal damage. The present study compares the ACLT-MX-model with the more recently

introduced Groove-model on longitudinal measurements of osteophyte formation and gait as a surrogate marker of pain and disability, in addition to structural endpoint parameters. METHODS: Degenerative joint damage was induced Labrador dogs according to the ACLT-MX-model (n=7) or Groove-model (n=7). Every 4 weeks radiographs were taken to analyze osteophyte formation. Every 2 weeks gait was recorded using force-plate analysis. Joints were analyzed for features of degeneration 12 weeks after surgery. RESULTS: Both models showed similar osteophyte formation and gait changes for both experimental and contra-lateral control joints, although more pronounced for the ACLT-MX-model. This was supported by the structural endpoint measurements. Cartilage integrity, chondrocyte activity and synovial inflammation revealed similar characteristics of degenerative joint disease in both groups, again more pronounced in the ACLT-MX-model. CONCLUSIONS: The ACLT-MX-model demonstrates characteristics of joint degeneration that are related to moderate to severe osteoarthritis with clear synovial inflammatory activity. The Groove-model is a less painful and a significantly milder model of joint degeneration. The latter model might be more suitable to study subtle changes as a result of intervention than the more robust ACLT-MX-model.

Descriptors: anterior cruciate ligament injuries, cartilage, articular physiology, joint instability physiopathology, osteoarthritis physiopathology, regeneration physiology, stifle physiology, anterior cruciate ligament pathology, arthralgia etiology, arthralgia physiopathology, cartilage, articular injuries, cartilage, articular pathology, chondrocytes pathology, dogs, gait physiology, inflammation, joint instability pathology, models, animal, osteophyte pathology.

Fujii, Y. (2003). **Treatment of diaphragmatic fatigue with inhaled aminophylline therapy in an experimental canine model: an open-label, dose-ranging, pharmacologic study.** *Current Therapeutic Research* 64(9): 725-732. ISSN: 0011-393X.

Abstract: Background: Diaphragmatic fatigue may contribute to the development of respiratory failure. Although aminophylline administered IV has been widely used to treat diaphragmatic fatigue, to date it has not been used in aerosol formulation for this purpose. Objective: The aim of this study was to assess the efficacy of inhaled aminophylline on contractility of fatigued diaphragm in an experimental canine model. Methods: This open-label, dose-ranging, pharmacologic study was conducted at the Department of Anesthesiology, University of Tsukuba Institute of Clinical Medicine, Tsukuba (Ibaraki, Japan). Diaphragmatic fatigue was induced in healthy, male, mongrel dogs by intermittent supramaximal bilateral electrophrenic stimulation at a low frequency (20 Hz) applied for 30 minutes. Immediately after the end of the fatigue-producing period, group 1 received inhaled vehicle only, group 2 received inhaled aminophylline 12.5 mg/mL, group 3 received inhaled aminophylline 25 mg/mL, and group 4 was infused with verapamil 0.1 mg/kgcntdotmin during inhalation of aminophylline 25 mg/mL. Diaphragmatic contractility was assessed using transdiaphragmatic pressure (Pdi). Results: Twenty-eight dogs were used in the study (7 dogs were assigned to each treatment group). When fatigue was established, Pdi at low-frequency stimulation decreased significantly from baseline in all groups (all $P < 0.05$), and no significant change in Pdi was found at high-frequency stimulation. In groups 2 and 3, during aminophylline inhalation, Pdi at 20-Hz stimulation increased significantly from fatigued values (both $P < 0.05$). Pdi increased significantly more in group 3 than in group 2

(P < 0.05). In group 4, infusion of verapamil offset the increase in Pdi seen with aerosolized aminophylline in fatigued diaphragm. The integrated electrical activity of the diaphragm did not change significantly in any group. Conclusions: Inhaled aminophylline significantly improved contractility of fatigued diaphragm in a dose-related manner in this experimental canine model (P < 0.05). Its potent effect ay be caused by transmembrane calcium movement.

Descriptors: nervous system, neural coordination, pharmacology, diaphragmatic fatigue, muscle disease, drug therapy, dose ranging pharmacologic study, open label.

Fukuroku, J., N. Inoue, B. Rafiee, F.H. Sim, F.J. Frassica, and E.Y. Chao (2007). **Extracortical bone-bridging fixation with use of cortical allograft and recombinant human osteogenic protein-1.** *Journal of Bone and Joint Surgery. American Volume* 89(7): 1486-96. ISSN: 0021-9355.

Abstract: BACKGROUND: Prosthetic reconstruction with extracortical bone-bridging fixation is an effective method for the treatment of massive bone loss. We evaluated the effect of the use of recombinant human osteogenic protein-1 (rhOP-1) combined with allogenic cortical bone strips as a substitute for an autogenous bone graft for extracortical bone-bridging. METHODS: Eight skeletally mature adult male dogs underwent a bilateral resection of a 6-cm segment of the femoral diaphysis and reconstruction with a porous segmental prosthesis. On the experimental side, an allogenic cortical onlay graft in the form of bone strips combined with rhOP-1 mixed with bovine type-I-collagen putty (OP-1 putty) was applied. On the control side, allogenic cortical bone strips augmented with autogenous cancellous bone chips and bone marrow were used. The reconstructions were followed for twelve weeks with biweekly evaluations of load-bearing gait and radiographs. The animals were killed twelve weeks after the surgery, and the reconstructed femora were studied biomechanically, histologically, and with microradiographs. RESULTS: One animal was excluded from the analysis because a fracture of the proximal part of the femur on the control side was observed radiographically twelve weeks after the surgery. There were no significant differences in load-bearing gait between the experimental and control sides throughout the experimental period. Serial radiographs revealed a 1.9-fold (p<0.04), 2.7-fold (p<0.01), and 2.4-fold (p<0.03) increase in mineralized area on the experimental side at two, four, and six weeks, respectively. The torsional stiffness and strength of the fixation attributed to the extracortical bridging bone alone were 2.3-fold (p<0.03) and 2.2-fold (p=0.058) greater on the experimental side, respectively. The allograft porosity on the experimental side was 3.8-fold (p<0.02) greater than that on the control side. With the number of samples available, there was no significant difference in mineral apposition rate between the experimental and control sides. CONCLUSIONS: In an animal model of segmental bone-replacement prosthetic fixation with use of the extracortical bone-bridging principle, an allogenic onlay cortical graft combined with rhOP-1 was an effective substitute for autogenous bone graft.

Descriptors: bone morphogenetic proteins pharmacology, bone transplantation, femur surgery, prostheses and implants, transforming growth factor beta pharmacology, biomechanics, bone morphogenetic protein 7, dogs, femur radiography, models, animal, osseointegration, prosthesis design, transplantation, homologous, weight bearing.

Gilbert, T.W., A. Nieponice, A.R. Spievack, J. Holcomb, S. Gilbert, and S.F. Badylak (2008). **Repair of the thoracic wall with an extracellular matrix scaffold in a canine model.** *Journal of Surgical Research* 147(1): 61-7. ISSN: 0022-4804.

Abstract: Naturally derived extracellular matrix (ECM) scaffolds have been successfully used to promote constructive remodeling of injured or missing tissue in a variety of anatomical locations, including abdominal wall repair. Furthermore, ECM scaffolds have shown the ability to resist infection and adhesion formation. The present study investigated the utility of an ECM scaffold, specifically, porcine urinary bladder matrix (UBM), for repair of a 5 x 5 cm full-thickness lateral thoracic wall defect in a canine model (n = 6) including 5-cm segments of the 6th and 7th rib. The resected portion of the 7th rib was replaced as an interpositional graft along with the UBM scaffold. As a control, a Gore-Tex patch was used to repair the same defect (n = 2). The control animals healed by encapsulation of the Gore-Tex patch by dense collagenous tissue. The remodeled UBM grafts showed the presence of site-specific tissue, including organized fibrous connective tissue, muscle tissue, adipose tissue, and bone. Upon fluoroscopic examination, it was shown that both bony defects were replaced with new calcified bone. In the 6th rib space, new bone bridged the entire span. In the 7th rib space, there was evidence of bone formation between the interpositional graft and the existing bone, as well as de novo formation of organized bone in the shape of the missing rib segment parallel to the interpositional graft. This study shows that a naturally occurring ECM scaffold promotes site-specific constructive remodeling in a large thoracic wall defect.

Descriptors: extracellular matrix transplantation, surgical mesh, thoracic wall surgery, bone regeneration, dogs, fluoroscopy, models, animal, swine, urinary bladder.

Gilbert, T.W., A.M. Stewart Akers, A. Simmons Byrd, and S.F. Badylak (2007). **Degradation and remodeling of small intestinal submucosa in canine Achilles tendon repair.** *Journal of Bone and Joint Surgery. American Volume* 89(3): 621-30. ISSN: 0021-9355.

Abstract: BACKGROUND: Extracellular matrix derived from porcine small intestinal submucosa is used for the repair of musculotendinous tissues. Preclinical evaluation and clinical use have suggested that small intestinal submucosa extracellular matrix degrades rapidly after implantation and can be replaced by host tissue that is functionally and histologically similar to the normal tissue. METHODS: The present study analyzed the temporal degradation of a ten-layer multilaminate device of small intestinal submucosa extracellular matrix used for the repair of canine Achilles tendon and examined the corresponding histological appearance of the remodeled tissue during the course of scaffold degradation. Devices were fabricated from small intestinal submucosa extracellular matrix labeled with 14C. The amount of 14C remaining in the remodeled graft was measured by liquid scintillation counting at three, seven, fourteen, twenty-eight, sixty, and ninety days after surgery. Blood, urine, feces, and other parenchymal tissues were also harvested to determine the fate of scaffold degradation products. Tissue specimens were prepared for routine histological analysis to examine the morphology of the remodeled graft at each time-point. RESULTS: The small intestinal submucosa extracellular matrix graft degraded rapidly, with approximately 60% of the mass lost by one month after surgery, and the graft was completely resorbed by three months after surgery. The graft supported rapid cellular infiltration and host tissue ingrowth. By ninety days after surgery, the remodeled small intestinal submucosa extracellular matrix consisted of a dense collagenous tissue with organization, cellularity, and vascularity similar to that of

normal tendon. CONCLUSIONS: Small intestinal submucosa extracellular matrix is rapidly degraded after implantation for the repair of a musculotendinous tissue in this canine Achilles tendon repair model and is replaced by the deposition and organization of host tissue that is histologically similar to that of normal tissue.
Descriptors: achilles tendon physiology, extracellular matrix transplantation, intestinal mucosa transplantation, achilles tendon cytology, achilles tendon injuries, carbon radioisotopes, dogs, extracellular matrix physiology, intestinal mucosa cytology, intestine, small cytology, models, animal, swine, transplantation, heterologous.

Gill, A.B. (2008). **Transplantation of entire bones with their joint surface: A. Bruce Gill MD (1876-1965). The 6th president of the AAOS 1937.** *Clinical Orthopaedics and Related Research* 466(1): 47-9. ISSN: 0009-921X.
Descriptors: bone transplantation history, joints surgery, bone transplantation methods, dogs, history, 19th century, history, 20th century, models, animal, orthopedics history.

Green, S.L., J.M. Westendorf, H. Jaffe, H.C. Pant, L.C. Cork, E.A. Ostrander, F. Vignaux, and J.E.J. Ferrell (2005). **Allelic variants of the canine heavy neurofilament (NFH) subunit and extensive phosphorylation in dogs with motor neuron disease.** *Journal of Comparative Pathology* 132(1): 33-50. ISSN: 0021-9975.
NAL Call Number: 41.8 J82
Abstract: Aberrant accumulation of extensively phosphorylated heavy (high molecular weight) neurofilament (NFH) and neurodegeneration are features of hereditary canine spinal muscular atrophy (HCSMA), an animal model of human motor neuron disease. In this study, the canine NFH gene was mapped, cloned, and sequenced, and electrospray/mass spectrometry was used to evaluate the phosphorylation state of NFH protein from normal dogs and dogs with HCSMA. The canine NFH gene was localized to a region on canine chromosome 26 that corresponds to human NFH on chromosome 22q. The predicted length of the canine NFH protein is 1135 amino acids, and it shares an 80.3% identity with human NFH and >74.6% with murine NFH proteins. Direct sequencing of NFH cDNA from HCSMA dogs revealed no mutations, although cDNA sequence and restriction fragment length polymorphism (RFLP) analysis indicates that there are at least three canine NFH alleles, differing in the position and number (61 or 62) of Lys-Ser-Proline (KSP) motifs. The two longest alleles (L1 and L2), each with 62 KSP repeats, contain an additional 24-base insert and were observed in both normal and HCSMA dogs. However, the shorter allele (the C allele), with 61 KSP sites and lacking the 24-base insertion, was absent in dogs with HCSMA. Mass spectrometry data indicated that almost all of the NFH KSP phosphorylation sites were occupied. No new or extra sites were identified in native NFH purified from the HCSMA dogs. The predominance of the two longest NFH alleles and the additional KSP phosphorylation sites they confer probably account for the presence of extensively phosphorylated NFs detected immunohistochemically in dogs with HCSMA.
Descriptors: animal model, human motor neuron disease, genetics, hereditary canine spinal muscular atrophy (HCSMA), neurodegeneration .
Notes: Library: National-Library-of-Medicine.

Green, S.L., D.M. Bouley, M.J. Pinter, L.C. Cork, and G.T. Vatassery (2001). **Canine motor neuron disease: clinicopathologic features and selected indicators of oxidative stress**. *Journal of Veterinary Internal Medicine* 15(2): 112-119. ISSN: 0891-6640.

NAL Call Number: SF601.J65

Abstract: Hereditary canine spinal muscular atrophy (HCSMA) is an inherited motor neuron disease affecting a kindred of Brittanies. We have examined the clinicopathologic abnormalities in 57 animals with HCSMA, including 43 affected adult dogs and 14 homozygote pups. We also measured selected biochemical indices of oxidative stress: serum vitamin E (alpha-tocopherol) and Se concentrations; serum concentrations of Cu, Zn, Mg, and Fe; and total superoxide dismutase and glutathione peroxidase activities in red blood cells. Dogs with HCSMA had the following abnormalities: regenerative anemia, hypoglobulinemia, hypochloremia, and abnormally high creatine kinase and liver alkaline phosphatase activities. Serum Cu concentration was significantly (P = .01) increased in adult dogs with HCSMA compared to control dogs. Serum vitamin E concentrations tended to be lower in adult dogs with HCSMA compared to controls, and were significantly (P = .01) lower in homozygote pups compared to control pups.

Descriptors: veterinary medicine, medical sciences, neural coordination, hereditary canine spinal muscular atrophy, nervous system disease, motor neuron disease, muscle disease, clinicopathologic features, oxidative stress.

Hannafin, J.A., S.P. Arnoczky, A. Hoonjan, and P.A. Torzilli (1995). **Effect of stress deprivation and cyclic tensile loading on the material and morphologic properties of canine flexor digitorum profundus tendon: an in vitro study**. *Journal of Orthopaedic Research* 13(6): 907-914. ISSN: 0736-0266.

Abstract: The effect of stress deprivation and cyclic tensile loading on the mechanical and histologic properties of the canine flexor digitorum profundus tendon was examined using an in vitro system. Stress deprivation resulted in a progressive and statistically significant decrease in the tensile modulus over an 8-week period. Histologically, stress-deprived tendons demonstrated quantitative changes in the morphology and number of cells and in the alignment of collagen. The change in tensile properties was not associated with an alteration in the water content of the tissue, but the change appeared to be dependent on the presence of a viable cell population. Dead (acellular) tendons did not undergo any alteration in tensile modulus in this in vitro system. In vitro cyclic tensile loading of tendons over a 4-week time period resulted in a significant increase in the tensile modulus (93% of the control) compared with that of the stress-deprived tendons (68% of the control). This loading regimen also maintained the normal histologic pattern of the tendons. The results of this study are similar to those previously reported for in vivo studies and suggest that this in vitro model may represent a valid system with which to test the effects of various stress conditions on the tensile properties of tissues.

Descriptors: biochemistry and molecular biophysics, cell biology, muscular system, movement and support, skeletal system, movement and support, collagen, immobilization, orthopedics, photomicrograph, viable cell population.

Hoshino, M., T. Egi, H. Terai, T. Namikawa, and K. Takaoka (2007). **Regenerative repair of long intercalated rib defects using porous cylinders of beta-tricalcium phosphate: an experimental study in a canine model.** *Plastic and Reconstructive Surgery* 119(5): 1431-9.

Abstract: BACKGROUND: In maxillofacial, spinal, and orthopedic surgery, bony ribs have been used as a source of donor bone. The resultant defects are not usually repaired, despite the pain or cosmetic morbidity experienced by the patient. The authors evaluated the efficacy of an osteoconductive beta-tricalcium phosphate and the contribution of the periosteum in rib bone regeneration. METHODS: Two 8-cm-long intercalated rib defects were generated in each of 30 beagle dogs. In the first group (n = 15), one defect was implanted with 16 small, short, porous beta-tricalcium phosphate cylinders that were connected with a titanium wire, and the other defect was left untreated. In the remaining 15 dogs, the periosteum was devitalized by ethanol, and then the same surgical procedures were performed. Each group was subdivided into three groups (n = 5), and the animals were euthanized at 3, 6, and 12 weeks. Bone regeneration was assessed radiologically, histologically, and mechanically. RESULTS: In the defect implanted with beta-tricalcium phosphate on intact periosteum, newly formed bone was present on and in the beta-tricalcium phosphate cylinders and bridged both ends of the resected ribs at 12 weeks, with replacement of beta-tricalcium phosphate by new bone. Mechanical testing of these ribs revealed that they had 70 percent of the strength of normal ribs when compared in a bending stress test at 12 weeks after surgery. No regenerative bone bridging the rib defects was seen in the ethanol-devitalized or untreated groups. CONCLUSIONS: Porous beta-tricalcium phosphate cylinders placed in tandem on the intact periosteum might be useful for the repair of rib bone donated at surgery, presenting a new and unique method for regenerating rib defects.

Descriptors: biocompatible materials, bone regeneration, calcium phosphates, prostheses and implants, ribs surgery, dogs, materials testing, models, animal, porosity, prosthesis design.

Jakobsen, T., J. Baas, J.E. Bechtold, B. Elmengaard, and K. Soballe (2007). **Soaking morselized allograft in bisphosphonate can impair implant fixation.** *Clinical Orthopaedics and Related Research* 463: 195-201. ISSN: 0009-921X.

Abstract: The use of impacted, morselized allograft is a well-established way to provide initial stability of revision joint replacements. We investigated whether rinsing morselized allograft in bisphosphonate and subsequently impacting it around experimental titanium-coated implants would further facilitate biomechanical implant fixation and graft incorporation. In 10 dogs, a pair of titanium implants surrounded by a 2.5-mm gap was inserted into the proximal part of each humerus during two separate surgeries to allow two observation periods. The gap was filled with impacted, morselized allograft soaked in either bisphosphonate (alendronate, 2 mg/mL) or saline (control). Unbound alendronate was not rinsed away. During the first surgery, one pair of implants (alendronate and control) was inserted into one humerus. Eight weeks later, a second pair of implants was inserted into the contralateral humerus. The first pair of implants was observed for 12 weeks and the second pair for 4 weeks. Implants were evaluated by histomorphometry and biomechanical pushout test. We found substantially decreased biomechanical implant fixation for all implants surrounded by impacted, morselized allograft that had been soaked in alendronate. Furthermore, the alendronate treatment blocked formation of new bone and inhibited resorption of the graft

material. Although limited by the specific dose of alendronate used and the omission of rinsing away excess bisphosphonate, this study warrants caution and calls for further experimental research before impacting alendronate-soaked morselized allograft around clinical joint replacements.
Descriptors: alendronate adverse effects, arthroplasty, replacement methods, bone density conservation agents adverse effects, bone transplantation, osseointegration drug effects, prostheses and implants, prosthesis failure, arthroplasty, replacement instrumentation, biomechanics, dogs, humerus drug effects, humerus pathology, humerus surgery, models, animal, prosthesis design, titanium, transplantation, homologous.

Jakobsen, T., J. Baas, S. Kold, J.E. Bechtold, B. Elmengaard, and K. Soballe (2009). **Local bisphosphonate treatment increases fixation of hydroxyapatite-coated implants inserted with bone compaction.** *Journal of Orthopaedic Research Official Publication of the Orthopaedic Research Society* 27(2): 189-94.
Abstract: It has been shown that fixation of primary cementless joint replacement can independently be enhanced by either: (1) use of hydroxyapatite (HA) coated implants, (2) compaction of the peri-implant bone, or (3) local application of bisphosphonate. We investigated whether the combined effect of HA coating and bone compaction can be further enhanced with the use of local bisphosphonate treatment. HA-coated implants were bilaterally inserted into the proximal tibiae of 10 dogs. On one side local bisphosphonate was applied prior to bone compaction. Saline was used as control on the contralateral side. Implants were evaluated with histomorphometry and biomechanical push-out test. We found that bisphosphonate increased the peri-implant bone volume fraction (1.3-fold), maximum shear strength (2.1-fold), and maximum shear stiffness (2.7-fold). No significant difference was found in bone-to-implant contact or total energy absorption. This study indicates that local alendronate treatment can further improve the fixation of porous-coated implants that have also undergone HA-surface coating and peri-implant bone compaction.
Descriptors: alendronate pharmacology, bone density conservation agents pharmacology, coated materials, biocompatible, durapatite, osseointegration drug effects, prostheses and implants, dogs, materials testing, models, animal, shear strength drug effects, tibia drug effects, tibia surgery, titanium.

Jensen, T.B., O. Rahbek, S. Overgaard, and K. Soballe (2004). **Platelet rich plasma and fresh frozen bone allograft as enhancement of implant fixation - an experimental study in dogs**. *Journal of Orthopaedic Research* 22(3): 653-658. ISSN: 0736-0266.
Descriptors: blood and lymphatics, transport and circulation, skeletal system, movement and support, surgery, medical sciences, bone grafting, clinical techniques, therapeutic and prophylactic techniques, implant fixation, clinical techniques, titanium alloy implant, prosthetic, bone formation, enhancement, gap healing, enhancement .

Kwack, K.S., J.H. Cho, M.S. Kim M, C.S. Yoon, Y.S. Yoon, J.W. Choi, J.W. Kwon, B.H. Min, J.S. Sun, and S.Y. Kim (2008). **Comparison study of intraarticular and intravenous gadolinium-enhanced magnetic resonance imaging of cartilage in a canine model.** *Acta Radiologica Stockholm, Sweden 1987* 49(1): 65-74.
Abstract: BACKGROUND: Magnetic resonance (MR) imaging and measurement of gly-

cosaminoglycan (GAG) have potential for characterization of hyaline articular cartilage. Recently, some reports have demonstrated the potential of direct administration of contrast media for MR imaging of cartilage. PURPOSE: To prove the feasibility of intraarticular gadolinium-enhanced MR imaging of cartilage (iGEMRIC) and T1 relaxation mapping of the articular cartilage in vivo with intraarticular injection of Gd-DTPA2-. MATERIAL AND METHODS: Five healthy beagle dogs underwent MR imaging and T1 relaxation mapping of the knee joints of both hind legs. The delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) and iGEMRIC techniques were interchanged with MR imaging. For dGEMRIC, a double routine dose of Gd-DTPA2- (0.2 mM/kg) was administered intravenously. For iGEMRIC, 2.5 and 1.25 mmol/l saline-diluted Gd-DTPA2- solutions were separately injected into the right and left knee joints, respectively, prior to MR imaging. Color-coded T1 maps of 20 femoral condyles were obtained from the dGEMRIC and iGEMRIC images. The signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and glycosaminoglycan (GAG) delineation of articular cartilage were compared between the dGEMRIC and iGEMRIC techniques. RESULTS: The mean SNR was higher with dGEMRIC than with iGEMRIC, but the difference was not statistically significant (P=0.174). The mean (+/-SD) CNR was higher with iGEMRIC (-11.6+/-3.4) than with dGEMRIC (-16.7+/-4.0; P=0.000), although the absolute value of the CNR was higher with dGEMRIC. The layering and gradient distribution of GAG were more clearly visualized on the iGEMRIC images. The mean scores of GAG delineation with dGEMRIC and iGEMRIC were 0.7+/-0.6 and 2.2+/-1.7, respectively. The iGEMRIC method better visualized GAG distribution (P=0.001). CONCLUSION: Although the SNR did not differ significantly between the iGEMRIC and dGEMRIC techniques, the color-coded T1 map produced with iGEMRIC allowed better cartilage evaluation. Thus, iGEMRIC exhibits the useful features of both MR arthrography and dGEMRIC, and provides a color-coded T1 map that is useful for diagnosing early articular cartilage damage.
Descriptors: cartilage, articular anatomy and histology, contrast media administration and dosage, gadolinium dtpa administration and dosage, hindlimb anatomy and histology, image enhancement methods, magnetic resonance imaging methods, dogs, dose response relationship, drug, feasibility studies, glycosaminoglycans analysis, image processing, computer assisted, injections, intra articular, injections, intravenous, models, animal, sensitivity and specificity.

Lahm, A., P.C. Kreuz, A. El Tayeh, E. Mrosek, M. Oberst, J. Haberstroh, and H. Merk (2007). **Loss of zonal organization of articular cartilage after experimental subchondral trauma of the knee joint.** *Saudi Medical Journal* 28(4): 649-52. ISSN: 0379-5284.
Descriptors: bone and bones injuries, cartilage, articular injuries, cartilage, articular pathology, knee joint pathology, dogs, imaging, three dimensional, magnetic resonance imaging, models, animal, osteoarthritis, knee pathology.

Lahm, A., M. Uhl, M. Edlich, C. Erggelet, J. Haberstroh, and P.C. Kreuz (2005). **An experimental canine model for subchondral lesions of the knee joint.** *The Knee* 12(1): 51-5. ISSN: 0968-0160.
Abstract: Aim of the study was to create an animal model for the investigation of the role of subchondral bone damage without initial cartilage lesion in the pathogenesis of osteoar-

thritis, the mechanical properties of the joints as well as its role in cartilage metabolism. Therefore, after cadaver studies an animal model was created to apply a transarticular load to the femoro-patellar joint under reproducible conditions and produce a pure subchondral damage without affecting the articular cartilage. Following the cadaver studies a first group of four dogs was impacted to identify forces to produce isolated subchondral fractures in the femoral condyle. Then a second group of 12 dogs knee joints was impacted under identical conditions with forces of approximately 2100 N to produce similar subchondral fractures without cartilage damage in one joint under MRI control: T1-weighted SE-sequences. T2-weighted TSE, fat suppressed TIRM-sequences and 3D-FLASH fat saturated sequences. FLASH 3D-sequences revealed intact cartilage after impact in all cases and TIRM-sequences showed subchondral fractures representing bleeding, microfractures and fragmented bone trabecules. Turbo spin echo sequences and T1-weighted images revealed other intact intraarticular structures such as ligaments and menisci. The proposed experimental animal model is suitable to investigate the effect of pure subchondral damage on the articular cartilage and on means of treatment of cartilage defects without surgical intervention and without initial cartilage damage.
Descriptors: animal model. subchondral lesions, subchondral bone damage, cartilage lesion, pathogenesis, osteoarthritis.
Notes: Library: National-Library-of-Medicine.

Lahm, A., M. Uhl, C. Erggelet, J. Haberstroh, and E. Mrosek (2004). **Articular cartilage degeneration after acute subchondral bone damage: an experimental study in dogs with histopathological grading.** *Acta Orthopaedica Scandinavica* 75(6): 762-7. ISSN: 0001-6470.
Abstract: BACKGROUND: Subchondral fracture patterns and bone bruises have been described and some clinical studies have shown alterations in the initially healthy cartilage after such lesions. METHODS AND RESULTS: After having performed cadaver studies, we created an animal model to produce pure subchondral damage without affecting the articular cartilage, under MRI control. We used 12 beagle dogs. For quantification of different degrees of staining, we used a grading of the sections by means of the HHGS (Histological-Histochemical Grading System) or Mankin score. RESULTS: In all cases, FLASH 3D sequences revealed intact cartilage in MRI after impact. The best detection of subchondral fractures was achieved in fat-suppressed TIRM sequences. Image analysis based on the HHGS showed changes in 10 of 12 samples, with a high degree of significance 6 months after the initial trauma. Correlation analysis showed loss of the physiological distribution of proteoglycans and glycoproteins in the different zones of articular cartilage. Subcategories "Structure", "Cells" and "Safranin-O Staining" also showed high significance, and the category "Tidemark Integrity" showed a tendency. INTERPRETATION: Our findings indicate that acute subchondral fractures are a predictor of degenerative changes within 6 months. Modifications and supplements to rehabilitation might be needed in cases with accompanying subchondral lesions, e.g. in ACL tears.
Descriptors: animal model, beagle dogs, subchondral damage, articular cartilage, rehabilitation.

Lahm, A., M. Uhl, H.A. Lehr, C. Ihling, P.C. Kreuz, and J. Haberstroh (2004). **Photoshop-based image analysis of canine articular cartilage after subchondral damage.** *Archives of Orthopaedic and Trauma Surgery* 124(7): 431-6. ISSN: 0936-8051.

Abstract: INTRODUCTION: The validity of histopathological grading is a major problem in the assessment of articular cartilage. Calculating the cumulative strength of signal intensity of different stains gives information regarding the amount of proteoglycan, glycoproteins, etc. Using this system, we examined the medium-term effect of subchondral lesions on initially healthy articular cartilage. MATERIALS AND METHODS: After cadaver studies, an animal model was created to produce pure subchondral damage without affecting the articular cartilage in 12 beagle dogs under MRI control. Quantification of the different stains was provided using a Photoshop-based image analysis (pixel analysis) with the histogram command 6 months after subchondral trauma. RESULTS: FLASH 3D sequences revealed intact cartilage after impact in all cases. The best detection of subchondral fractures was achieved with fat-suppressed TIRM sequences. Semiquantitative image analysis showed changes in proteoglycan and glycoprotein quantities in 9 of 12 samples that had not shown any evidence of damage during the initial examination. Correlation analysis showed a loss of the physiological distribution of proteoglycans and glycoproteins in the different zones of articular cartilage. CONCLUSION: Currently available software programs can be applied for comparative analysis of histologic stains of hyaline cartilage. After subchondral fractures, significant changes in the cartilage itself occur after 6 months.

Descriptors: beagle dogs, animal model, subchondral damage, proteoglycan, glycoproteins, histologic stains, hyaline cartilage.

Lee, C.R., A.J. Grodzinsky, H.P. Hsu, and M. Spector (2003). **Effects of a cultured autologous chondrocyte-seeded type ii collagen scaffold on the healing of a chondral defect in a canine model.** *Journal of Orthopaedic Research* 21(2): 272-281. ISSN: 0736-0266.

Abstract: Using a previously established canine model for repair of articular cartilage defects, this study evaluated the 15-week healing of chondral defects (i.e., to the tidemark) implanted with an autologous articular chondrocyte-seeded type II collagen scaffold that had been cultured in vitro for four weeks prior to implantation. The amount and composition of the reparative tissue were compared to results from our prior studies using the same animal model in which the following groups were analyzed: defects implanted with autologous chondrocyte-seeded collagen scaffolds that had been cultured in vitro for approximately 12 h prior to implantation, defects implanted with autologous chondrocytes alone, and untreated defects. Chondrocytes, isolated from articular cartilage harvested from the left knee joint of six adult canines, were expanded in number in monolayer for three weeks, seeded into porous type II collagen scaffolds, cultured for an additional four weeks in vitro and then implanted into chondral defects in the trochlear groove of the right knee joints. The percentages of specific tissue types filling the defects were evaluated histomorphometrically and certain mechanical properties of the repair tissue were determined. The reparative tissue filled 88+-6% (mean+-SEM; range 70-100%) of the cross-sectional area of the original defect, with hyaline cartilage accounting for 42+-10% (range 7-67%) of defect area. These values were greater than those reported previously for untreated defects and defects implanted with a type II collagen scaffold seeded with autologous chondrocytes within 12 h prior to implantation. Most striking, was the decreased amount of fibrous tissue filling the defects in the current

study, 5+-5% (range 0-26%) as compared to previous treatments. Despite this improvement, indentation testing of the repair tissue formed in this study revealed that the compressive stiffness of the repair tissue was well below (20-fold lower stiffness) that of native articular cartilage.
Descriptors: animal model, bone disease, repair, articular cartilage defects, chondral defects, autologous chondrocyte seeded type ii collagen scaffold, prosthetic, implantat, clinical techniques, therapeutic and prophylactic techniques.

Libicher, M., M. Ivancic, V. Hoffmann, and W. Wenz (2005). **Early changes in experimental osteoarthritis using the Pond-Nuki dog model: technical procedure and initial results of in vivo MR imaging.** *European Radiology* 15(2): 390-4. ISSN: 0938-7994.
NAL Call Number: R895.A1
Abstract: The purpose of this study was to prove the feasibility of combining in vivo MR imaging with the Pond-Nuki animal model for the evaluation of osteoarthritis. In an experimental study, 24 beagle dogs underwent transection of the anterior cruciate ligament of the left leg (modified Pond-Nuki model). The dogs were randomly assigned into four groups and examined by MRI after 6, 12, 24 and 48 weeks. MR imaging of both knees was performed under general anesthesia with the contralateral joint serving as control. In group 1 (6 weeks postoperatively), the first sign detected on MRI was subchondral bone marrow edema in the posteromedial tibia. After 12 weeks, erosion of the posteromedial tibial cartilage could be observed, followed by meniscus degeneration and osteophytosis after 24 and 48 weeks. The contralateral knee joint showed transient joint effusion, but no significant signs of internal derangement (P<0.001). By combining in vivo MR imaging with the Pond-Nuki model, it is possible to detect early signs of osteoarthritis. The first sign was posteromedial subchondral bone marrow edema in the tibia followed by progressive cartilage degeneration and joint derangement. The in vivo model therefore seems to be suitable for longitudinal studies or monitoring the therapeutic effects of osteoarthritis.
Descriptors: animal model, beagle dogs, osteoarthritis, transection of the anterior cruciate ligament, in vivo model, progressive cartilage degeneration, joint derangement, therapeutic effects.
Notes: Library: National-Library-of-Medicine.

Lopez, M.J., D. Kunz, R.J. Vanderby, D. Heisey, J. Bogdanske, and M.D. Markel (2003). **A comparison of joint stability between anterior cruciate intact and deficient knees: a new canine model of anterior cruciate ligament disruption.** *Journal of Orthopaedic Research* 21(2): 224-230. ISSN: 0736-0266.
Abstract: Transection of the canine anterior cruciate ligament (ACL) is a well-established osteoarthritis (OA) model. This study evaluated a new method of canine ACL disruption as well as canine knee joint laxity and joint capsule (JC) contribution to joint stability at two time points (16 and 26 weeks) after ACL disruption (n=5/time interval). Ten crossbreed hounds were evaluated with force plate gait analysis and radiographs at intervals up to 34 weeks after monopolar radiofrequency energy (MRFE) treatment of one randomly selected ACL. Each contralateral ACL was sham treated. The MRFE treated ACLs ruptured approximately eight weeks (mean 52.5 days, SEM+-1.0, range 48-56 days) after treatment. Gait analysis and radiographic changes were consistent with established canine ACL transec-

tion models of OA. Anterior-posterior (AP) translation and medial-lateral (ML) rotation were measured in each knee at 30degree, 60degree, and 90degree of flexion with and then without JC with loads of 40 N in AP translation and 4 Nm in ML rotation. A statistically significant interaction in AP translation included JC by cruciate (P=0.02), and there was a trend for a cruciate by time (P=0.07) interaction. Significant interactions in ML rotational testing included the presence of joint capsule (P=0.0001) and angle by cruciate (P=0.0012). This study describes a model in which canine ACLs predictably rupture approximately eight weeks after arthroscopic surgery and details the contribution of JC to canine knee stability in both ACL intact and deficient knees. The model presented here avoids the introduction of potential surgical variables at the time of ACL rupture and may contribute to studies of OA pathogenesis and inhibition. This model may also be useful for insight into the pathologic changes that occur in the knee as the ACL undergoes degeneration prior to rupture.
Descriptors: methods and techniques, skeletal system, movement and support, anterior cruciate ligament degeneration, bone disease, anterior cruciate ligament rupture, knee joint laxity, joint disease, osteoarthritis, joint disease, etiology, arthroscopic surgery, clinical techniques, therapeutic and prophylactic techniques, force plate gait analysis, clinical techniques, monopolar radiofrequency energy treatment, radiography, diagnostic techniques, anterior posterior translation, medial lateral rotation.

Lopez, M.J. and M.D. Markel (2003). **Anterior cruciate ligament rupture after thermal treatment in a canine model.** *American Journal of Sports Medicine* 31(2): 164-167. ISSN: 0363-5465.
Abstract: Background: The use of radiofrequency energy to treat damaged anterior cruciate ligaments is gaining popularity. However, complete rupture of the ligament after treatment has been reported. Purpose: To evaluate the effect of thermal energy applied arthroscopically to normal, intact anterior cruciate ligaments in mature dogs. Study Design: Controlled laboratory study. Methods: Monopolar radiofrequency energy was applied to the normal anterior cruciate ligament of 1 knee in 18 dogs. The contralateral anterior cruciate ligament (also normal) was sham treated. Force-plate gait analysis was performed preoperatively and at 4, 8, 12, 16, 26, and 36 weeks after surgery. Anterior cruciate ligament rupture was detected by a sudden onset of nonweightbearing and a positive drawer sign. Results: All treated ligaments ruptured approximately 55 days after surgery (mean, 55 days; standard error, 1.6). Conclusions: Although monopolar radiofrequency energy may have some potential in the treatment of lax anterior cruciate ligaments, in the application described here the result was a highly predictable deterioration and rupture of all treated anterior cruciate ligaments. Clinical Relevance: On the basis of these findings, we strongly recommend that strict selection and application criteria be used when considering use of this modality on anterior cruciate ligaments that are stretched or partially disrupted, or both. Use of this modality should be followed by adherence to a highly conservative rehabilitation protocol.
Descriptors: methods and techniques, skeletal system, movement and support, anterior cruciate ligament rupture, connective tissue disease, radiofrequency energy treatment, clinical techniques, therapeutic and prophylactic techniques.

Marin, C., R. Granato, M. Suzuki, J.N. Gil, A. Piattelli, and P.G. Coelho (2008). **Removal torque and histomorphometric evaluation of bioceramic grit-blasted/acid-etched and dual acid-etched implant surfaces: an experimental study in dogs.** *Journal of Periodontology* 79(10):

1942-9. ISSN: 0022-3492.

Abstract: BACKGROUND: Surface modifications to dental implants have been used in an attempt to accelerate the osseointegration process. The objective of this study was to biomechanically/histomorphometrically evaluate a bioceramic grit-blasted and acid-etched surface (BGB/AA; test) versus a dual acid-etched implant surface (control) in a beagle dog model. METHODS: Control and BGB/AA implants were subjected to a series of physicochemical characterization tools, including scanning electron microscopy (SEM), atomic force microscopy (AFM), and auger photoelectron spectroscopy (APS). The animal model included the placement of 72 implants along the proximal tibiae of six beagle dogs, which remained in place for 2 or 4 weeks. After euthanization, half of the specimens were biomechanically tested (removal torque), and the other half was non-decalcified processed to slides of approximately 30 microm thickness for histomorphologic and histomorphometric (percentage of bone-to-implant contact [%BIC]) evaluation. Analysis of variance at the 95% confidence level and the Tukey post hoc test were used for multiple comparisons. RESULTS: SEM and AFM showed that surface microtextures were qualitatively and quantitatively different and that the BGB/AA surface presented higher submicrometer average roughness values (R(a)) and root mean square (RMS) values compared to control surfaces. Ca and P were detected at the BGB/AA surface by APS. Higher degrees of bone organization were observed along the perimeter of the BGB/AA surface compared to control, despite the non-significant differences in %BIC between the surfaces (P >0.25). Significantly higher removal torque was observed for the BGB/AA implants at both time periods (P <0.0001). CONCLUSION: According to the biomechanical and histomorphologic results, early biomechanical fixation was positively affected by the BGB/AA surface compared to the dual-acid etched surface.

Descriptors: acid etching, dental methods, biocompatible materials chemistry, ceramics chemistry, dental etching methods, dental implants, torque, biomechanics, bone remodeling physiology, calcium analysis, carbon analysis, dental prosthesis design, dogs, electron probe microanalysis, materials testing, microscopy, atomic force, microscopy, electron, scanning, models, animal, osseointegration physiology, oxygen analysis, phosphorus analysis, surface properties, tibia pathology, tibia surgery, titanium analysis.

Martel, J., A. Bueno, M.P. Dominguez, P. Llorens, J. Quiros, and C. Delgado (2008). **Percutaneous radiofrequency ablation: relationship between different probe types and procedure time on length and extent of osteonecrosis in dog long bones.** *Skeletal Radiology* 37(2): 147-52. ISSN: 0364-2348.

NAL Call Number: RC78.A1

Abstract: PURPOSE: We have been using radiofrequency ablation for the percutaneous treatment of osteoid osteoma since 2001. Frequently, lesions are located near the joint surface, involve the vertebral body or are close to major nerves. We seek to determine whether radiofrequency ablation (RFA) can be used safely in these cases. MATERIALS AND METHODS: A total of 65 lesions were induced in 4 dogs. Each dog underwent RFA on the diaphysis of long bones, as well as femoral and humeral heads. Four different sessions were carried out by using 1- and 2-cm probes with or without a cool-tip system and by varying the timing of the procedure. Plain film, CT, and MRI were obtained. All bone samples were examined histologically. RESULTS: The dogs' activity after the procedure was normal. No pathologic fractures occurred despite unrestricted activity of the animals. Cortical bone was

always respected; therefore, articular cartilage has not been damaged. Radiological findings were characteristic. There were no significant differences in lesion size, probe type, and the duration of the procedure. The mean lesion diameter perpendicular to the electrode was 18.5 mm. CONCLUSIONS: Our study confirms the insulative effect of cortical bone. RFA can be safely performed close to the joint surface without damaging the cartilage.
Descriptors: catheter ablation adverse effects, catheter ablation instrumentation, joint diseases prevention and control, leg bones pathology, leg bones radiography, osteonecrosis etiology, catheter ablation methods, dogs, femur head pathology, femur head radiography, humerus pathology, humerus radiography, leg bones injuries, magnetic resonance imaging, models, animal, osteonecrosis prevention and control, severity of illness index, time factors, tomography, x ray computed.

Meisel, H.J., T. Ganey, and W. Hutton (2003). **Disc chondrocyte transplantation in a canine model: a treatment for degenerated or damaged intervertebral disc.** *International Journal of Artificial Organs* 26(9): 870. ISSN: 0391-3988.
Descriptors: cell biology, skeletal system, movement and support, intervertebral disc damage, bone disease, therapy, intervertebral disc degeneration, bone disease, therapy, disc chondrocyte transplantation, laboratory techniques, therapeutic and prophylactic techniques.

Murray, C., F. Markos, H.M. Snow, T. Corcoran, N. Parfrey, and G.D. Shorten (2003). **Effects of fenoldopam on renal blood flow and its function in a canine model of rhabdomyolysis.** *European Journal of Anaesthesiology* 20(9): 711-718. ISSN: 0265-0215.
Abstract: Background and objective: Our hypothesis was that fenoldopam, a selective DA1 agonist, would protect against rhabdomyolysis-induced renal injury. Methods: We studied the effects of intravenous fenoldopam (0. 1-1.0 mug kg-1 min-1) or saline on renal blood flow and function in 10 anaesthetized Labrador dogs in whom rhabdomyolysis and myoglobinuric acute renal failure had been induced by administration of glycerol 50% (10 mL kg-1) intramuscularly. Haemodynamic measurements including renal blood flow and derived parameters of renal function including creatinine clearance were recorded before and for the 30 min following glycerol injection, and during the 3 h following commencement of each infusion. Serum malondialdehyde concentrations were measured before and 15 min after glycerol intramuscularly, and 30 and 150 min after commencement of the infusion. Results: In the fenoldopam group, creatinine clearance was less than placebo at 1 and 2 h after commencing the infusion (12.7+-11.5 versus 31.3+-9.9 mL min-1, P=0.04; 8.5+-5.3 versus 20.1+-7.4 mL min-1, P=0.03). A 140-fold increase in serum malondialdehyde concentration occurred in one dog (fenoldopam group). Conclusion: Fenoldopam increased the severity of the renal injury in this canine model of myoglobinuric acute renal failure.
Descriptors: muscular system, movement and support, pharmacology, urinary system, chemical coordination and homeostasis, myoglobinuric acute renal failure, urologic disease, renal injury, injury, urologic disease, rhabdomyolysis, muscle disease, hemodynamics, renal blood flow, renal function.

Narmoneva, D.A., H.S. Cheung, J.Y. Wang, D.S. Howell, and L.A. Setton (2002). **Altered swelling behavior of femoral cartilage following joint immobilization in a canine model**. *Journal of Orthopaedic Research* 20(1): 83-91. ISSN: 0736-0266.

Abstract: Periods of reduced joint loading have been shown to induce changes in the biochemical composition, metabolism and mechanics of articular cartilage. In this study, changes in cartilage swelling behavior were studied following a 4-week period of joint immobilization, using a recently developed osmotic loading technique (J. Biomech. 32 (1999) 401-408). The magnitude and distribution of swelling strains were measured in cartilage-bone samples equilibrated in physiological and hypotonic saline, relative to a hypertonic reference NaCl solution. Physicochemical parameters (glycosaminoglycan fixed charge density and water volume fraction) were determined in site-matched cartilage samples. The experimental data for swelling strains, fixed charge density and water volume fraction were used with a triphasic mechano-chemical theory (J. Biomech. Eng. 113 (1991) 245-258) to determine the effect of joint immobilization on the tensile modulus of the cartilage solid matrix. Four weeks of immobilization resulted in a significant increase in the magnitude of swelling-induced strains, and a significant decrease in fixed charge density in cartilage, as compared with the contralateral controls. Joint immobilization also resulted in decreases in values for the modulus of cartilage, as compared with the contralateral controls. Our results suggest that 4 weeks of joint immobilization had a significant effect on cartilage mechanical function that may be linked to collagen changes in the cartilage extracellular matrix.
Descriptors: methods and techniques, skeletal system, movement and support, osteoarthritis, joint disease, therapy, joint immobilization, therapeutic method, osmotic loading technique, therapeutic method, cartilage swelling behavior, swelling strain, distribution, magnitude, tensile modulus, water volume fraction.

Nehrer, S., H.A. Breinan, A. Ramappa, G. Young, S. Shortkroff, L.K. Louie, C.B. Sledge, I.V. Yannas, and M. Spector (1997). **Matrix collagen type and pore size influence behaviour of the seeded canine chondrocytes**. *Biomaterials* 18(11): 769-776. ISSN: 0142-9612.
NAL Call Number: R857.M3B48
Abstract: This study directly compared the behaviour of chondrocytes in porous matrices comprising different collagen types and different pore diameters. There was a dramatic difference in the morphology of the cells in the type I and type II collagen matrices. The cells in the type II collagen matrix retained their chondrocytic morphology and synthesized glycosaminoglycans, while in the type I matrix the chondrocytes displayed a fibroblastic morphology with less biosynthetic activity than those in the type II. Small pore diameter affected morphology initially in the type I matrices and showed a higher increase of DNA content, but with time the cells lost the chondrocytic morphology. Our results demonstrate the marked influence of collagen type and pore characteristics on the phenotypic expression of seeded chondrocytes.
Descriptors: biochemistry and molecular biophysics, cell biology, genetics, metabolism, methods and techniques, skeletal system, movement and support, adult, behavior, biobusiness, biomaterials, cartilage defect treatment, cartilage repair, chondrocyte, chondrocytic morphology, collagen, collagen pore size, dna, glycosaminoglycans, matrix collagen type, medical research, mongrel, phenotypic expression, porous matrices, seeded canine chondrocytes, skeletal system, tissue engineering.

Ohyama, T., Y. Kubo, H. Iwata, and W. Taki (2002). **Beta-tricalcium phosphate as a substitute for autograft in interbody fusion cages in the canine lumbar spine**. *Journal of Neurosurgery* 97(3 Supplement): 350-354. ISSN: 0022-3085.

Abstract: Object: An interbody fusion cage has been introduced for cervical anterior interbody fusion. Autogenetic bone is packed into the cage to increase the rate of union between adjacent vertebral bodies. Thus, donor site-related complications can still occur. In this study a synthetic ceramic, beta-tricalcium phosphate (TCP), was examined as a substitute for autograft bone in a canine lumbar spine model. Methods: In 12 dogs L-1 to L-4 vertebrae were exposed via a posterolateral approach, and discectomy and placement of interbody fusion cages were performed at two intervertebral disc spaces. One cage was filled with autograft (Group A) and the other with TCP (Group B). The lumbar spine was excised at 16 weeks postsurgery, and biomechanical, microradiographic, and histological examinations were performed. Both the microradiographic and histological examinations revealed that fusion occurred in five (41.7%) of 12 operations performed in Group A and in six (50%) of 12 operations performed in Group B. The mean percentage of trabecular bone area in the cages was 54.6% in Group A and 53.8% in Group B. There were no significant intergroup differences in functional unit stiffness. Conclusions: Good histological and biomechanical results were obtained for TCP-filled interbody fusion cages. The results were comparable with those obtained using autograft-filled cages, suggesting that there is no need to harvest iliac bone or to use allo- or xenografts to increase the interlocking strength between the cage and vertebral bone to achieve anterior cervical interbody fusion.

Descriptors: biomaterials, equipment, apparatus, devices and instrumentation, skeletal system, movement and support, cervical anterior interbody fusion, therapeutic method, interbody fusion cages, medical equipment, autograft .

Pearce, A.I., R.G. Richards, S. Milz, E. Schneider, and S.G. Pearce (2007). **Animal models for implant biomaterial research in bone: a review.** *European Cells and Materials* 13: 1-10.

NAL Call Number: R857.M3 E97

Abstract: Development of an optimal interface between bone and orthopaedic and dental implants has taken place for many years. In order to determine whether a newly developed implant material conforms to the requirements of biocompatibility, mechanical stability and safety, it must undergo rigorous testing both in vitro and in vivo. Results from in vitro studies can be difficult to extrapolate to the in vivo situation. For this reason the use of animal models is often an essential step in the testing of orthopaedic and dental implants prior to clinical use in humans. This review discusses some of the more commonly available and frequently used animal models such as the dog, sheep, goat, pig and rabbit models for the evaluation of bone-implant interactions. Factors for consideration when choosing an animal model and implant design are discussed. Various bone specific features are discussed including the usage of the species, bone macrostructure and microstructure and bone composition and remodelling, with emphasis being placed on the similarity between the animal model and the human clinical situation. While the rabbit was the most commonly used of the species discussed in this review, it is clear that this species showed the least similarities to human bone. There were only minor differences in bone composition between the various species and humans. The pig demonstrated a good likeness with human bone however difficulties may be encountered in relation to their size and ease of handling. In this respect the

dog and sheep/goat show more promise as animal models for the testing of bone implant materials. While no species fulfils all of the requirements of an ideal model, an understanding of the differences in bone architecture and remodelling between the species is likely to assist in the selection of a suitable species for a defined research question.
Descriptors: bone substitutes, implants, experimental, materials testing, models, animal, bone remodeling, bone and bones anatomy and histology, dogs, goats anatomy and histology, rabbits, sheep anatomy and histology, swine anatomy and histology.

Pinter, M.J., R.F. Waldeck, N. Wallace, and L.C. Cork (1995). **Motor unit behavior in canine motor neuron disease**. *Journal of Neuroscience* 15(5 PART 1): 3447-3457. ISSN: 0270-6474.
NAL Call Number: RC346
Abstract: Hereditary canine spinal muscular atrophy (HCSMA) is an autosomally dominant disease of motor neurons that shares many pathological features with human motor neuron disease. A particularly striking feature of the affected, accelerated phenotype (homozygous HCSMA) is that profound weakness develops before appreciable motor neuron cell death occurs (Cork et al., 1989a), implying that motor unit functional defects occur initially. The purpose of this study was to identify the site of these defects and characterize their nature. In most young homozygotes (2-3 months postnatal), motor neurons were encountered that could support orthodromic action potential propagation to the muscle but did not activate muscle fibers. The tetanic forces of innervated motor units in young homozygotes tended to be smaller than those in closely age-matched clinically normal animals. In older homozygotes (apprxeq 4.5 months, postnatal), all motor neurons sampled were capable of activating muscle fibers, but many motor units displayed abnormal behavior including an inability to sustain force output during high frequency activation. Motor units exhibiting tetanic failure also showed proportionately greater twitch potentiation than nonfailing units of similar unpotentiated twitch amplitude. Tetanic failure and large potentiation tended to occur in motor units that possessed the slowest contraction speeds. These results indicate that motor neuron functional defects in HCSMA appear initially in the most distal parts of the motor axon and involve defective neurotransmission. The possible roles of distal nerve degeneration, motor terminal sprouting, and synaptic transmission in causing these deficits are considered.
Descriptors: genetics, muscular system, movement and support, nervous system, neural coordination, hereditary spinal muscle atrophy, motor terminal sprouting, nerve degeneration, synaptic transmission.

Por, Y.C., C.R. Barcelo, K.E. Salyer, D.G. Genecov, K. Troxel, E. Gendler, M.E. Elsalanty, and L.A. Opperman (2007). **Bone generation in the reconstruction of a critical size calvarial defect in an experimental model.** *Annals of the Academy of Medicine, Singapore* 36(11): 911-9. ISSN: 0304-4602.
Abstract: OBJECTIVE: This study was designed to investigate the optimal combination of known osteogenic biomaterials with shape conforming struts to achieve calvarial vault reconstruction, using a canine model. METHODS: Eighteen adolescent beagles were divided equally into 6 groups. A critical size defect of 6 x 2 cm traversed the sagittal suture. The biomaterials used for calvarial reconstruction were demineralised perforated bone matrix (DBM), recombinant human bone morphogenetic protein-2 (rhBMP2) and autogenous

platelet-rich plasma (PRP). The struts used were cobalt chrome (metal) or resorbable plate. The groupings were as follows: 1) DBM + metal, 2) DBM + PRP + metal, 3) DBM + PRP + resorbable plate, 4) DBM + rhBMP2 + metal, 5) DBM + rhBMP2 + PRP + metal, and 6) DBM + rhBMP2 + resorbable plate. Animals were euthanised at 3 months post-surgery. There was no mortality or major complications. Analysis was performed macroscopically, histologically, and with computed tomography (CT). RESULTS: There was complete bony regeneration in the rhBMP2 groups only. Non-rhBMP2 groups had minimal bony ingrowth from the defect edges and on the dural surface, a finding confirmed by CT scan and histology. PRP did not enhance bone regeneration. Shape conformation was good with both metal and resorbable plate. CONCLUSION: rhBMP2 but not PRP accelerated calvarial regeneration in 3 months. The DBM in the rhBMP2 groups were substituted by new trabecular bone. Shape molding was good with both metal and resorbable plate.
Descriptors: bone regeneration physiology, models, animal, skull pathology, biocompatible materials, bone morphogenetic proteins pharmacology, dogs, postoperative care, recombinant proteins pharmacology, reconstructive surgical procedures, skull growth and development, skull surgery, transforming growth factor beta pharmacology.

Qi, C. and H. Changlin (2007). **Levels of biomarkers correlate with magnetic resonance imaging progression of knee cartilage degeneration: a study on canine.** *Knee Surgery, Sports Traumatology, Arthroscopy Official Journal of the ESSKA* 15(7): 869-78. ISSN: 0942-2056.
Abstract: To examine the association between levers of cartilage oligomeric matrix protein (COMP), matrix metalloproteinases-1 (MMP-1), matrix metalloproteinases-3 (MMP-3), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) in serum and synovial fluid, and MR imaging of cartilage degeneration in knee joint, and to understand the effects of movement training with different intensity on cartilage of knee joint. 20 adult canines were randomly divided into three groups (8 in the light training group; 8 in the intensive training group; 4 in the control group), and canines of the two training groups were trained daily at different intensity. The training lasted for 10 weeks in all. Magnetic resonance imaging (MRI) examinations were performed regularly (2, 4, 6, 8, 10 week) to investigate the changes of articular cartilage in the canine knee, while concentrations of COMP, MMP-1, MMP-3, TIMP-1 in serum and synovial fluid were measured by ELISA assays. We could find imaging changes of cartilage degeneration in both the training groups by MRI examination during training period, compared with the control group. However, there was no significant difference between these two training groups. Elevations of levels of COMP, MMP-1, MMP-3, TIMP-1, MMP-3/TIMP-1 were seen in serum and synovial fluid after training, and their levels had obvious association with knee MRI grades of cartilage lesion. Furthermore, there were statistically significant associations between biomarkers levels in serum and in synovial fluid. Long-time and high-intensity movement training induces cartilage degeneration in knee joint. Within the intensity extent applied in this study, knee cartilage degeneration caused by light training or intensive training has no difference in MR imaging, but has a comparatively obvious difference in biomarkers level. To detect articular cartilage degeneration in early stage and monitor pathological process, the associated application of several biomarkers has a very good practical value, and can be used as a helpful supplement to MRI.
Descriptors: cartilage, articular pathology, knee joint pathology, magnetic resonance imaging, physical conditioning, animal methods, biological markers metabolism, dogs,

enzyme linked immunosorbent assay, extracellular matrix proteins metabolism, glycoproteins metabolism, knee joint metabolism, matrix metalloproteinase 1 metabolism, matrix metalloproteinase 3 metabolism, models, animal, random allocation, synovial fluid metabolism, tissue inhibitor of metalloproteinase 1 metabolism.

Rogachefsky, R.A., R.D. Altman, M.S. Markov, and H.S. Cheung (2004). **Use of a permanent magnetic field to inhibit the development of canine osteoarthritis**. *Bioelectromagnetics* 25(4): 260-270. ISSN: 0197-8462.

Abstract: This study was designed to determine the potential of a permanent magnetic field to inhibit the progression of osteoarthritis (OA) in a canine model. The magnetic field was created by 72 domino-sized ceramic magnets with surface field strength of 1100 G (0.11 T). The magnetic field strength at the surface of the mattress was 450-500 G (45-50 mT) and was equally distributed over the mattress surface. Eighteen animals had closed resection of their right stifle anterior cruciate ligament. Their kennel floors were covered in one of three ways: no floor mattress (OA) (N = 6); a floor mattress with domino-sized ceramic pieces placed between two layers of foam (sham control OA-MAT) (N = 6); or a floor mattress with domino-sized ceramic permanent magnets placed between two layers of foam (OA-MAT-MAG) (N = 6). Animals were kept in their cages except for 4 h of exercise each day. The left stifle of six animals served as the normal control. The stifle joints were examined at 12 weeks for synovial effusion, gross anatomic appearance, microscopic anatomic appearance (Mankin score), and metalloproteinase (MMP)-1 and -3. Macroscopically, the OA-MAT-MAG group appeared to have less synovitis, less synovial effusion, less disruption of the cartilage surface, and less cartilage ulceration than did the OA group or the control mattress group. The mean Mankin score for the OA-MAT-MAG group was less than that for the OA group (4.2 +/- 0.8 vs. 6.7 +/- 0.3; P < .05) and the control mattress group (4.2 +/- 0.8 vs. 5.2 +/- 0.8; P > .05), but greater than that for the normal left group (4.2 +/- 0.8 vs. 1.0 +/- 0.4; P < .05). These scores show a trend of improvement for OA-MAT-MAG group but the difference with the sham control OA-MAT group was not statistically significant. In immunohistochemical studies, the OA-MAT-MAG group cartilage was stained less heavily for MMP-1 and MMP-3 than were the OA group cartilage and the control mattress group cartilage, but did not differ significantly in MMP-1 and MMP-3 from the normal left group cartilage. The OA-MAT-MAG group did not differ from the normal left group in MMP-3 as determined by Western blot analysis. The study suggests that OA of the medial femoral condyle developed in a canine model exposed to a magnetic field may be inhibited beyond the benefit provided by mattress. Further studies are needed to delineate more precisely the effect of the magnetic field in reducing the severity of OA.

Descriptors: enzymology, biochemistry and molecular biophysics, methods and techniques, skeletal system, movement and support, osteoarthritis, joint disease, diagnosis, radiotherapy, therapy, western blot analysis, genetic techniques, laboratory techniques, permanent magnetic field exposure, applied and field techniques.

Schulmerich, M.V., J.H. Cole, K.A. Dooley, M.D. Morris, J.M. Kreider, S.A. Goldstein, S. Srinivasan, and B.W. Pogue (2008). **Noninvasive Raman tomographic imaging of canine bone tissue.** *Journal of Biomedical Optics* 13(2): 020506. ISSN: 1083-3668.

Abstract: Raman spectroscopic diffuse tomographic imaging has been demonstrated for

the first time. It provides a noninvasive, label-free modality to image the chemical composition of human and animal tissue and other turbid media. This technique has been applied to image the composition of bone tissue within an intact section of a canine limb. Spatially distributed 785-nm laser excitation was employed to prevent thermal damage to the tissue. Diffuse emission tomography reconstruction was used, and the location that was recovered has been confirmed by micro-computed tomography (micro-CT) images.
Descriptors: image enhancement methods, image interpretation, computer assisted methods, spectrum analysis, raman methods, tibia anatomy and histology, tomography, optical methods, dogs, models, animal.

Shimatsu, Y., K. Katagiri, T. Furuta, M. Nakura, and et al. (2003). **Canine x-linked muscular dystrophy in japan (cxmdj).** *Experimental Animals (Tokyo)* 52(2): 93-97. ISSN: 1341-1357.
NAL Call Number: QL55. J55
Abstract: The purpose of this study was to develop a strain of canine X-linked muscular dystrophy (CXMD), a model of Duchenne muscular dystrophy, in Japan. A female beagle was artificially inseminated with frozen-thawed spermatozoa derived from an affected golden retriever. Subsequently, two carrier female dogs (G1 carriers) and four normal male littermates were produced. Thereafter, the two G1 carriers were mated with beagle sires. As a result, each bitch whelped three times, and out of 54 pups, 17 affected male descendants, and 11 carrier female descendants (G2 carriers) were detected. One G2 carrier was then mated with a beagle sire and 15 pups in two whelpings were produced, including five affected males and four carrier females (G3 carriers). A total of 10 female beagles were artificially inseminated to evaluate the fertility of the frozen-thawed spermatozoa from the two affected dogs. The whelping rates of the two affected dogs were 4/5 and the litter sizes were 5.0+-1.41 and 6.0+-0.82, respectively. These results indicate that a canine X-linked muscular dystrophy colony has been established in Japan. We called them CXMDJ.
Descriptors: genetics, muscular system, movement and support, veterinary medicine, medical sciences, Duchenne muscular dystrophy, muscle disease, nervous system disease, canine X linked muscular dystrophy, genetic disease, artificial insemination, laboratory techniques.

Skurla, C.P., G.E. Pluhar, D.J. Frankel, E.L. Egger, and S.P. James (2005). **Assessing the dog as a model for human total hip replacement. Analysis of 38 canine cemented femoral components retrieved at post-mortem.** *The Journal of Bone and Joint Surgery. British Volume* 87(1): 120-7. ISSN: 0301-620X.
Abstract: Post-mortem retrieval of canine, cemented femoral components was analysed to assess the performance of these implants in the dog as a model for human total hip replacement (THR). Mechanical testing and radiological analysis were performed to determine the stability of the implant and the quality of the cement. Thirty-eight implants from 29 dogs were retrieved after time intervals ranging from 0.67 to 11.67 years. The incidence of aseptic loosening was 63.2%, much higher than in human patients (6% in post-mortem studies). Failure of the femoral implants began with debonding at the cement-metal interface, similar to that in implants in man. The incidence of aseptic loosening was much lower in bilateral than in unilateral implants. Significant differences were observed for three different designs of implant. While the dog remains the animal model of choice for THR, results from this study

provide insight into interspecies differences in the performance of implants. For example, the performance of THR in dogs should be compared with that in young rather than in elderly human patients.
Descriptors: animal model, post-mortem, age differences, total hip replacement, hip implants, cemented femoral components, aseptic loosening, performance analysis.

Sumner, D.R., T.M. Turner, R.M. Urban, T. Turek, H. Seeherman, and J.M. Wozney (2004). **Locally delivered rhbmp-2 enhances bone ingrowth and gap healing in a canine model.** *Journal of Orthopaedic Research* 22(1): 58-65. ISSN: 0736-0266.
Abstract: The purpose of the present study was to determine if recombinant human bone morphogenetic protein-2 (rhBMP-2) enhances bone ingrowth into porous-coated implants and gap healing around the implants. In the presence of a 3-mm gap between the implant and host bone, porous-coated implants were placed bilaterally for four weeks in the proximal humeri of skeletally mature, adult male dogs. In three treatment groups, the test implant was treated with HA/TCP and rhBMP-2 in buffer at a dose of 100 mug/implant (n=5), 400 mug/implant (n=6), or 800 mug/implant (n=5) and placed in the left humerus. In these same animals, an internal control implant was treated only with HA/TCP and buffer and placed in the right humerus. These groups were compared with a previously reported external control group of seven animals in which no growth factor was delivered (J. Orthop. Res. 19 (2001) 85). The BMP treated implants in the two lower dose groups had significantly more bone ingrowth than the external controls with the greatest effect in the 100 g/implant group (a 3.5-fold increase over the external control, p=0.008). All three dose groups had significantly more bone formation in the 3-mm gap surrounding the BMP treated implants than the external controls with the greatest effect in the 800 mug group (2.9-fold increase, p<0.001). Thus, application of rhBMP-2 to a porous-coated implant stimulated local bone ingrowth and gap healing. The enhancement of bone formation within the implant (bone ingrowth) was inversely related to dose.
Descriptors: pharmacology, skeletal system, movement and support, bone ingrowth, gap healing.

Tanaka, T., C. Zhao, Y.L. Sun, M.E. Zobitz, K.N. An, and P.C. Amadio (2007). **The effect of carbodiimide-derivatized hyaluronic acid and gelatin surface modification on peroneus longus tendon graft in a short-term canine model in vivo.** *Journal of Hand Surgery* 32(6): 876-81. ISSN: 0363-5023.
Abstract: PURPOSE: We have recently reported that application of carbodiimide-derivatized hyaluronic acid and gelatin (cd-HA gelatin) to a peroneus longus tendon graft increased tendon graft gliding ability and decreased work of flexion compared with untreated grafts in a canine model in vivo. In this study, we investigated the effect of this modification on adhesions, stiffness, strength of the distal attachment, and fibroblast count. METHODS: A total of 24 dogs were used for this study. The peroneus longus tendons of each hind leg were grafted into the 2nd and 5th digits of one forepaw in each dog. One peroneus longus tendon was treated with cd-HA gelatin prior to grafting, and the other one was immersed in 0.9% saline solution as a control. Animals were killed 1, 3, or 6 weeks postoperatively. RESULTS: The adhesion score of cd-HA gelatin-treated tendons was significantly less than that in the saline-treated tendons at all time points. There was no significant difference in the indenta-

tion stiffness between HA- and saline-treated grafts at any time point. For the ultimate force at the distal attachment, there was a significant difference among the time points, with a steady increase over time, but no significant difference between treated and control tendons at any time point. There was no significant difference in fibroblast count between treated and control tendons at any time point. CONCLUSIONS: Although gross adhesion formation was less, there was no significant difference in strength at the distal tendon-bone interface, cellularity, or tendon graft stiffness when comparing saline-treated and cd-HA gelatin-treated tendon grafts in vivo.

Descriptors: adjuvants, immunologic pharmacology, ethyldimethylaminopropyl carbodiimide pharmacology, gelatin pharmacology, hyaluronic acid pharmacology, tendons transplantation, cell count, dogs, fibroblasts metabolism, models, animal, tendon injuries surgery, tensile strength, tissue adhesions pathology, tissue adhesions prevention and control, tissue transplantation methods.

Taylor, B.A., G.O. Okubadejo, A.A. Patel, M.R. Talcott, T. Imamura, N. Hu, and B.W. Cunningham (2008). **Evaluation of total disc arthroplasty: a canine model.** *American Journal of Orthopedics Belle Mead, N.J.* 37(4): E64-70.

Abstract: The study reported here was designed to examine the biomechanical and histopathologic properties of total disc arthroplasty (TDA) using a canine model. Thirty-seven dogs were divided into 3 groups (intact spine, fusion, TDA) and sacrificed either at study commencement or at 3 months. Results showed progressive fusion from 0 to 3 months in the fusion group. The TDA group maintained motion throughout this period. No neurologic complications were noted in either group. These results establish the canine as a model for future studies of TDA.

Descriptors: arthroplasty, replacement methods, intervertebral disk surgery, models, animal, prostheses and implants, arthroplasty, biomechanics, dogs, intervertebral disk physiopathology, prosthesis design, range of motion, articular, spinal fusion.

Thomopoulos, S., H. Matsuzaki, M. Zaegel, R.H. Gelberman, and M.J. Silva (2007). **Alendronate prevents bone loss and improves tendon-to-bone repair strength in a canine model.** *Journal of Orthopaedic Research Official Publication of the Orthopaedic Research Society* 25(4): 473-9. ISSN: 0736-0266.

Abstract: Previously we showed a loss of bone and a concomitant decrease in mechanical properties in the first 21 days after flexor tendon insertion site injury and repair in a canine model. The goal of this short-term study was to suppress bone loss after insertion site repair using alendronate in an attempt to prevent the reduction in biomechanical properties. Flexor tendons of the second and fifth digits of the right forelimbs of canines were injured and repaired. Dogs received a daily oral dose of alendronate (2 mg/kg). One digit in each dog also received a local dose of alendronate in the bone tunnel at the time of surgery. The repair was evaluated for bone mineral density (BMD) and biomechanical properties and compared to data from a previous study in which no alendronate was used. Alendronate was effective in protecting the distal phalanx from resorption during tendon-to-bone healing (BMD was 94 and 104% of control for systemic alendronate and for systemic plus local alendronate, respectively). Alendronate treatment prevented much of the decrease in ultimate load that occurs in the first 21 days. Without treatment, ultimate load was 42% of control. With sys-

temic alendronate treatment and systemic plus local alendronate treatment, ultimate load was 78 and 69% of control, respectively. Failure mode was significantly different when comparing alendronate treatment to repair alone. A lower incidence of suture pull through was found in alendronate treated dogs, suggesting less tendon degeneration. Ultimate load can be improved in association with preventing the bone loss that normally occurs during the early period following tendon-to-bone repair. These initial short-term data demonstrate the potential for a clinical treatment that could enhance tendon-to-bone healing.
Descriptors: alendronate pharmacology, bone density conservation agents pharmacology, bone resorption prevention and control, bone and bones physiology, tendons physiology, wound healing drug effects, biomechanics, bone density drug effects, bone density physiology, bone resorption physiopathology, bone and bones drug effects, dogs, dose response relationship, drug, metalloproteases metabolism, models, animal, tendon injuries physiopathology, tendons drug effects, wound healing physiology.

Thomopoulos, S., E. Zampiakis, R. Das, M.J. Silva, and R.H. Gelberman (2008). **The effect of muscle loading on flexor tendon-to-bone healing in a canine model.** *Journal of Orthopaedic Research Official Publication of the Orthopaedic Research Society* 26(12): 1611-7.
Abstract: Previous tendon and ligament studies have demonstrated a role for mechanical loading in tissue homeostasis and healing. In uninjured musculoskeletal tissues, increased loading leads to an increase in mechanical properties, whereas decreased loading leads to a decrease in mechanical properties. The role of loading on healing tissues is less clear. We studied tendon-to-bone healing in a canine flexor tendon-to-bone injury and repair model. To examine the effect of muscle loading on tendon-to-bone healing, repaired tendons were either cut proximally (unloaded group) to remove all load from the distal phalanx repair site or left intact proximally (loaded group). All paws were casted postoperatively and subjected to daily passive motion rehabilitation. Specimens were tested to determine functional properties, biomechanical properties, repair-site gapping, and bone mineral density. Loading across the repair site led to improved functional and biomechanical properties (e.g., stiffness for the loaded group was 8.2 +/- 3.9 versus 5.1 +/- 2.5 N/mm for the unloaded group). Loading did not affect bone mineral density or gapping. The formation of a gap between the healing tendon and bone correlated with failure properties. Using a clinically relevant model of flexor tendon injury and repair, we found that muscle loading was beneficial to healing. Complete removal of load by proximal transection resulted in tendon-to-bone repairs with less range of motion and lower biomechanical properties compared to repairs in which the muscle-tendon-bone unit was left intact.
Descriptors: bone and bones physiology, muscle, skeletal physiology, tendons physiology, wound healing physiology, biomechanics, bone density physiology, dogs, homeostasis physiology, models, animal, range of motion, articular physiology.

Turner, R.T., A. Maran, S. Lotinun, T. Hefferan, G.L. Evans, M. Zhang, and J.D. Sibonga (2001). **Animal models for osteoporosis.** *Reviews in Endocrine and Metabolic Disorders* 2(1): 117-27. ISSN: 1389-9155.
Abstract: Animal models will continue to be important tools in the quest to understand the contribution of specific genes to establishment of peak bone mass and optimal bone architecture, as well as the genetic basis for a predisposition toward accelerated bone loss in the

presence of co-morbidity factors such as estrogen deficiency. Existing animal models will continue to be useful for modeling changes in bone metabolism and architecture induced by well-defined local and systemic factors. However, there is a critical unfulfilled need to develop and validate better animal models to allow fruitful investigation of the interaction of the multitude of factors which precipitate senile osteoporosis. Well characterized and validated animal models that can be recommended for investigation of the etiology, prevention and treatment of several forms of osteoporosis have been listed in Table 1. Also listed are models which are provisionally recommended. These latter models have potential but are inadequately characterized, deviate significantly from the human response, require careful choice of strain or age, or are not practical for most investigators to adopt. It cannot be stressed strongly enough that the enormous potential of laboratory animals as models for osteoporosis can only be realized if great care is taken in the choice of an appropriate species, age, experimental design, and measurements. Poor choices will results in misinterpretation of results which ultimately can bring harm to patients who suffer from osteoporosis by delaying advancement of knowledge.

Descriptors: animal models, species differences, age differences, genetics, bone mass, osteoporosis, prevention, treatment.

Turner, T.M., R.M. Urban, D.J. Hall, and G.B. Andersson (2007). **Bone ingrowth through porous titanium granulate around a femoral stem: histological assessment in a six-month canine hemiarthroplasty model.** *Upsala Journal of Medical Sciences* 112(2): 191-7. ISSN: 0300-9734.

Abstract: The procedure of using of porous titanium granules for cementless fixation of a hip replacement femoral stem was studied in a hemiarthroplasty model in 10 canines for 6 months. A vibrating instrument was used to facilitate both the delivery and distribution of the irregularly shaped porous titanium granules into the femoral canal as well as the subsequent insertion of a titanium alloy stem into the intramedullary bed of granules. Histological examination revealed lamellar bone formation through the mantle of porous titanium granules in continuity with the surrounding cortex resulting in the formation of an integrated mantle of bone and titanium granulate around the prosthesis.

Descriptors: femur growth and development, models, animal, titanium, arthroplasty, replacement, hip, dogs, femur anatomy and histology, femur radiography, microscopy, electron, scanning, prosthesis design.

Wilson, J.R., N.A. Duncan, W.R. Giles, and R.B. Clark (2004). **A voltage-dependent k+ current contributes to membrane potential of acutely isolated canine articular chondrocytes**. *Journal of Physiology* 557(1): 93-104. ISSN: 0022-3751.

NAL Call Number: 447.8 J82

Abstract: The electrophysiological properties of acutely isolated canine articular chondrocytes have been characterized using patch-clamp methods. The'steady-state' current-voltage relationship (I-V) of single chondrocytes over the range of potentials from -100 to + 40 mV was highly nonlinear, showing strong outward rectification positive to the zero-current potential. Currents activated at membrane potentials negative to -50 mV were time independent, and the I-V from -100 to -60 mV was linear, corresponding to an apparent input resistance of 9.3 +/- 1.4 GOMEGA (n = 23). The outwardly rectifying current was sensitive to the K+

channel blocking ion tetraethylammonium (TEA), which had a 50% blocking concentration of 0.66 mM (at +50 mV). The 'TEA-sensitive' component of the outwardly rectifying current had time- and membrane potential-dependent properties, activated near -45 mV and was half-activated at -25 mV. The reversal potential of the 'TEA-sensitive' current with external K+ concentration of 5 mm and internal concentration of 145 mm, was - 84 mV, indicating that the current was primarily carried by K+ ions. The resting membrane potential of isolated chondrocytes (-38.1 +/- 1.4 mv, n = 19) was depolarized by 14.8 +/- 0.9 mV by 25 mM TEA, which completely blocked the K+ current of these cells. These data suggest that this voltage-sensitive K+ channel has an important role in regulating the membrane potential of canine articular chondrocytes.
Descriptors: biochemistry and molecular biophysics, skeletal system, movement and support, membrane potential.

Yuasa, K., M. Yoshimura, N. Urasawa, S. Ohshima, J.M. Howell, A. Nakamura, T. Hijikata, Y. Miyagoe Suzuki, and S. Takeda (2007). **Injection of a recombinant AAV serotype 2 into canine skeletal muscles evokes strong immune responses against transgene products.** *Gene Therapy* 14(17): 1249-60. ISSN: 0969-7128.
Abstract: Using murine models, we have previously demonstrated that recombinant adeno-associated virus (rAAV)-mediated microdystrophin gene transfer is a promising approach to treatment of Duchenne muscular dystrophy (DMD). To examine further therapeutic effects and the safety issue of rAAV-mediated microdystrophin gene transfer using larger animal models, such as dystrophic dog models, we first investigated transduction efficiency of rAAV in wild-type canine muscle cells, and found that rAAV2 encoding beta-galactosidase effectively transduces canine primary myotubes in vitro. Subsequent rAAV2 transfer into skeletal muscles of normal dogs, however, resulted in low and transient expression of beta-galactosidase together with intense cellular infiltrations in vivo, where cellular and humoral immune responses were remarkably activated. In contrast, rAAV2 expressing no transgene elicited no cellular infiltrations. Co-administration of immunosuppressants, cyclosporine and mycophenolate mofetil could partially improve rAAV2 transduction. Collectively, these results suggest that immune responses against the transgene product caused cellular infiltration and eliminated transduced myofibers in dogs. Furthermore, in vitro interferon-gamma release assay showed that canine splenocytes respond to immunogens or mitogens more susceptibly than murine ones. Our results emphasize the importance to scrutinize the immune responses to AAV vectors in larger animal models before applying rAAV-mediated gene therapy to DMD patients.
Descriptors: dependovirus genetics, gene therapy adverse effects, genetic vectors adverse effects, muscle, skeletal immunology, muscular dystrophy, animal therapy, muscular dystrophy, duchenne therapy, base sequence, calmodulin genetics, cyclosporine administration and dosage, dogs, dystrophin genetics, dystrophin metabolism, gene therapy methods, genetic engineering, genetic vectors genetics, immunosuppressive agents administration and dosage, injections, intramuscular, interferon gamma immunology, lymphocyte activation, mice, mice, inbred c57bl, models, animal, molecular sequence data, muscle fibers, skeletal immunology, muscle fibers, skeletal virology, muscular dystrophy, animal immunology, muscular dystrophy, duchenne immunology, parvoviridae infections immunology, rna, messenger analysis, reverse transcriptase polymerase chain reaction, species specificity, t lymphocytes,

cytotoxic immunology, transduction, genetic methods, transgenes, beta galactosidase genetics.

Zhao, C., Y.L. Sun, M.E. Zobitz, K.N. An, and P.C. Amadio (2007). **Enhancing the strength of the tendon-suture interface using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and cyanoacrylate.** *Journal of Hand Surgery* 32(5): 606-11. ISSN: 0363-5023.
Abstract: PURPOSE: Preventing gap or rupture is important to achieving a successful outcome after tendon repair. Weak sutures break; strong sutures fail by pull-out at the tendon-suture interface. In this study, we investigated the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and cyanoacrylate to enhance the strength of the tendon-suture interface. METHODS: Twenty-four canine flexor digitorum profundus tendons were used to test EDC and cyanoacrylate reinforcement methods, with 12 tendons in each group. A single-loop suture technique was used to test the tendon-suture interface strength. RESULTS: The mean ultimate strengths of the EDC group and the cyanoacrylate group were significantly higher than those of their respective control groups. The stiffness of the group with cyanoacrylate-augmented loops was significantly higher than that of its respective control group. There was no significant difference in stiffness between the 2 reinforcement methods. CONCLUSIONS: Our results suggest that tendon-suture interface reinforcement may improve the pull-out failure strength of a suture construct and thereby increase the effectiveness of stronger suture materials. Future studies might address the effects of different kinds and methods of reinforcement with various suture materials and constructs and in different tissues.
Descriptors: cyanoacrylates, ethyldimethylaminopropyl carbodiimide, suture techniques, sutures, tendon injuries surgery, dogs, injections, materials testing, models, animal, tensile strength.

Nervous System

Barros, G.A., M.E. Marques, and E.M. Ganem (2007). **The effects of intrathecal administration of betamethasone over the dogs' spinal cord and meninges.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(5): 361-5. ISSN: 0102-8650.
Abstract: PURPOSE: To determinate the potential clinical and histological changes due the injection of betamethasone, when administered into the canine intrathecal space. METHODS: Twenty one animals were included in a random and blind manner in the study. After general anesthesia, intrathecal puncture was performed and 1 ml of the random solution was injected. The G1 dogs received 0.9% saline solution, the G2 dogs received 1.75 mg betamethasone and the G3 dogs received 3.5 mg of betamethasone. The animals were clinically evaluated for 21 days and then sacrificed. The lumbar and sacral portions of the spinal cord were removed for light microscopy histological analyses. RESULTS: No clinical changes were observed in any of the animals included in this study. No histological changes were observed in G1 animals. Inflammatory infiltration was observed in two dogs, one in G2, another in G3. Hemorrhage and necrosis were also seen in the G2 dog which inflammatory infiltration was detected. In other two dogs, one from G2 and another from G3, there was discreet fibrosis and thickness of the arachnoid layer which was focal in one and diffuse in the other. CONCLUSION: Intrathecal administration of betamethasone caused histological changes in the spinal cord and meninges in some of the dogs involved in this study.
Descriptors: anti inflammatory agents adverse effects, betamethasone adverse effects, meninges drug effects, spinal cord drug effects, analysis of variance, anti inflammatory agents administration and dosage, betamethasone administration and dosage, dogs, fibrosis etiology, inflammation chemically induced, inflammation pathology, injections, spinal, meninges pathology, models, animal, necrosis etiology, random allocation, sodium chloride administration and dosage, spinal cord pathology, spinal puncture.

Bashar, A.H., K. Suzuki, T. Kazui, M.Y. Okada, T. Suzuki, N. Washiyama, H. Terada, and K. Yamashita (2008). **Changes in cerebrospinal fluid and blood lactate concentrations after stent-graft implantation at critical aortic segment: a preliminary study.** *Interactive Cardiovascular and Thoracic Surgery* 7(2): 262-6.
Abstract: OBJECTIVES: Obstruction of blood flow through the arteria radicularis magna (ARM) has been linked with ischemic spinal cord injury after conventional thoracic aortic repair. Whether or not endoluminal stent-grafts, deliberately positioned against this artery can cause similar damage to the spinal cord has not been comprehensively investigated. The purpose of this study was to assess the blood and cerebrospinal fluid (CSF) concentrations of lactate - a well-known biochemical marker of ischemic neurological injury, before and after stent-graft implantation against the ARM. MATERIALS AND METHODS: Endoluminal stent-grafting was performed in ten mongrel dogs. In five animals (experimental group), stent-grafts covered the fourth and fifth lumbar segmental arteries - which have been described as the canine equivalents to the ARM in humans. In the remaining five animals (control group), devices of similar length were placed in the lower thoracic aorta. CSF was

obtained by cisternal puncture technique at the following time points; before stent-grafting, and 15, 30 and 60 min after stent-grafting. Parallel arterial blood samples were also obtained using a heparinized syringe. All samples were centrifuged and the supernatant analysed for lactate. RESULTS: The mean preprocedural lactate concentration in the CSF was 1.7+/-0.3 mmol/l. Mean postprocedural levels in the experimental group at 15, 30 and 60 min were 3.1+/-1.9, 3.9+/-1.1 and 11.9+/-2.5 mmol/l, respectively (control values; 2.1+/-1.9, 2.7+/-1.1 and 1.9+/-1.5 mmol/l, respectively). Mean preprocedural blood lactate level was 1.8+/-0.6 mmol/l, while the mean postprocedural concentrations in the experimental group at 15, 30 and 60 min were 2.9+/-1.2, 3.4+/-1.7 and 3.9+/-2.0 mmol/l, respectively. Two out of the five animals in the experimental group suffered mild to moderate hind limb weakness. CONCLUSION: Selective placement of stent-grafts against the ARM in dogs resulted in a conspicuous increase in CSF and blood lactate concentrations 60 min after the procedure with or without physical signs of neurological deficits. Although the small sample size of this preliminary study does not allow any definitive conclusion, it may be worthwhile to confirm the findings in appropriately controlled larger studies.

Descriptors: blood vessel prosthesis, blood vessel prosthesis implantation adverse effects, lactic acid metabolism, spinal cord ischemia etiology, stents, thoracic arteries surgery, aortography, biological markers metabolism, blood vessel prosthesis implantation instrumentation, dogs, lactic acid blood, lactic acid cerebrospinal fluid, models, animal, motor activity, pilot projects, prosthesis design, spinal cord ischemia metabolism, spinal cord ischemia physiopathology, thoracic arteries radiography, time factors, up regulation.

Bassiouni, H., R. Schulz, H. Dorge, D. Stolke, and G. Heusch (2007). **The impact of subarachnoid hemorrhage on regional cerebral blood flow and large-vessel diameter in the canine model of chronic vasospasm.** *Journal of Stroke and Cerebrovascular Diseases the Official Journal of National Stroke Association* 16(2): 45-51.

Abstract: OBJECTIVE: The aim of this study was to correlate changes in regional cerebral blood flow (rCBF) to the degree of cerebral vasospasm in the canine two-hemorrhage model of subarachnoid hemorrhage (SAH). METHODS: SAH was induced in 13 adult beagle dogs using the two-hemorrhage model. Eleven beagle dogs served as controls. Angiography of the basilar artery and measurements of rCBF with colored microspheres were performed on days 1 and 8. Diameter of the basilar artery was calculated at equidistant points from the angiogram. RESULTS: In controls, basilar artery diameter (mm) and rCBF (mL/min/g) were equal on days 1 and 8. In the SAH group, basilar artery diameter decreased significantly (1.27 +/- 0.17 [mean +/- SD]-0.84 +/- 0.15 mm). rCBF decreased significantly (P < .05) in the cerebrum (1.69 +/- 0.54 [mean +/- SD]-1.06 +/- 0.45 mL/min/g), cerebellum (1.18 +/- 0.40-0.80 +/- 0.32 mL/min/g), and brain stem (0.81 +/- 0.33-0.51 +/- 0.21 mL/min/g). However, decrements in CBF were not correlated to the reduction in vessel caliber in the corresponding vascular territory. CONCLUSION: Induced SAH in the canine model produces a significant impairment in rCBF irrespective of the degree of vasospasm of large cerebral vessels. The findings support the presumptive role of the microvasculature in regard to delayed cerebral ischemia after SAH.

Descriptors: cerebrovascular circulation, subarachnoid hemorrhage physiopathology, vasospasm, intracranial physiopathology, basilar artery pathology, blood flow velocity, brain

ischemia etiology, brain ischemia pathology, brain ischemia physiopathology, brain stem blood supply, cerebellum blood supply, dogs, microcirculation, microspheres, models, animal, renal circulation, telencephalon blood supply, vasospasm, intracranial complications, vasospasm, intracranial pathology.

Benczik, J., T. Seppala, M. Snellman, H. Joensuu, G.M. Morris, and J.W. Hopewell (2003). **Evaluation of the relative biological effectiveness of a clinical epithermal neutron beam using dog brain.** *Radiation Research* 159(2): 199-209. ISSN: 0033-7587.
NAL Call Number: 334.8 R11
Abstract: This investigation was designed to determine the relative biological effectiveness (RBE) of an epithermal neutron beam (FiR 1 beam) using the brains of dogs. The FiR 1 beam was developed for the treatment of patients with glioma using boron neutron capture therapy. Comparisons were made between the effects of whole-brain irradiation with epithermal neutrons and 6 MV photons. For irradiations with epithermal neutrons, three dose groups were used, 9.4+-0.1, 10.2+-0.1 and 11.5+-0.2 Gy. These physical doses were given as a single exposure and are quoted at the 90% isodose. Four groups of five dogs were irradiated with single doses of 10, 12, 14 or 16 Gy of 6 MV photons to the 100% isodose. Different reference isodoses were used to obtain the most comparable dose distribution in the brain for the two different irradiation modalities. Sequential magnetic resonance images (MRI) were taken for 77-115 weeks after irradiation to detect changes in the brain. Dose-effect relationships were established for changes in the brain as detected either by MRI or by subsequent gross morphology and histology. The doses that caused a specified response in 50% of the animals (ED50) were calculated from these dose-effect curves for each end point, and these values were used to calculate the RBE values for the different end points. The RBE values for the FiR 1 beam, based on changes observed on MRI, were in the range 1.2-1.3. For microscopic and gross pathological lesions, the values were in the range 1.2-1.4. The corresponding RBE values for the MRI and pathological end points for the high-LET components (protons from nitrogen capture and recoil protons from fast neutrons) were in the ranges 3.5-4.0 and 3.4-4.4, respectively. This assumed a dose-rate reduction factor of 0.6 for the low-dose-rate gamma-ray component of this beam. Finally, a comparison was made between experimentally derived photon doses, for a specified end point, with calculated photon equivalent doses, which were obtained using the weighting factors for clinical studies on the epithermal neutron beam on the Brookhaven Medical Research Reactor (BNL) in New York. This indicated that the radiation-induced lesions seen in the present study were, on average, detected at a 12% lower photon dose than predicted by the use of the BNL clinical weighting factors. This indicates the need for caution in the extrapolation of results from one reactor-based epithermal neutron beam to another.
Descriptors: methods and techniques, nervous system, neural coordination, radiation biology, magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, whole brain irradiation, epithermal neutron beam, relative biological effectiveness.

Bodine, R.E., S.E. Dow, G.D. Smith, and M.J. Kallman (2003). **A novel conscious dog model for monitoring electroencephalographic activity.** *FASEB Journal* 17(4-5): Abstract No. 153.8. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: nervous system, neural coordination, pharmacology, tremor, electroencephalography, non-invasive technique, monitoring , electroencephalographic activity.

Boehmer, L.N., M.F. Wu, J. John, and J.M. Siegel (2004). **Treatment with immunosuppressive and anti-inflammatory agents delays onset of canine genetic narcolepsy and reduces symptom severity**. *Experimental Neurology* 188(2): 292-299. ISSN: 0014-4886.
Descriptors: breeds, Doberman pinschers, Labrador retrievers, behavior, genetics, nervous system, neural coordination, pharmacology, genetic narcolepsy, behavioral and mental disorders, nervous system disease, therapy .

Brandes, I.F., A.G. Stucke, D. Jakovcevic, C. Dean, F.A. Hopp, E.J. Zuperku, and E.A. Stuth (2004). **Characteristics of the effects of locally applied serotonin on the discharge patterns of canine hypoglossal motoneurons (hmns) in vivo.** *FASEB Journal* 18(4-5): Abst. 468.8. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Abstract: Serotonin appears to play a key role in controlling the excitability of HMNs, which contributes to the maintenance of upper airway patency that may become compromised by sleep, anesthetics, potent analgesics and sedatives. The <I>in vivo</I> effects of serotonin on HMNs are incompletely understood. The purpose of this study was to characterize canine HMN responses to serotonin. Multibarrel micropipettes were used to simultaneously record unit activity and picoeject serotonin on HMNs in decerebrate, vagotomized, paralyzed, ventilated dogs. Spike-triggered averaging of hypoglossal nerve activity was used to verify that the recorded neuron was a HMN. Serotonin-induced changes in gain and offset of discharge patterns were analyzed. Dose-response effects were studied by progressive step increases in picoejection rate. Most HMNs displayed phasic activity during the inspiratory phase. As the serotonin dose-rate increased, HMN phasic activity markedly increased primarily through changes in gain (2X). At higher dose-rates, activity during the quiescent expiratory phase also increased resulting in a baseline shift. These results suggest that serotonin may act differentially by increasing the excitability of phasic glutamatergic inputs in most HMNs, while in other neurons it results in a tonic depolarization without gain changes or enhances tonic excitatory inputs. A combination of these two effects was also observed.Supported by NIH grant GM59234 and VA Med. Res. Funds.
Descriptors: biochemistry and molecular biophysics, nervous system, neural coordination.

Carlson, G.D., H.S. Oliff, C. Gorden, J. Smith, and P.A. Anderson (2003). **Cerebral spinal fluid pressure: effects of body position and lumbar subarachnoid drainage in a canine model.** *Spine* 28(2): 119-122. ISSN: 0362-2436.
Abstract: Study Design. This study used an in vivo model of subarachnoid cerebrospinal fluid pressure measurement. Objectives. To examine the relation between subarachnoid cerebrospinal fluid pressure in the cervical and lumbar spine and varying body positions, and

to test the hypothesis that increasing body inclination and lumbar subarachnoid drainage decreases cervical cerebrospinal fluid pressures. Summary of Background Data. Cerebrospinal fluid leaks are a recognized complication of anteriror posterior cervical surgery. Conflicting opinion exists regarding the benefits of postoperative patient positioning and lumbar subarachnoid drainage. Methods. Subarachnoid cerebrospinal fluid pressure of 7 beagles was monitored via two angiocatheters attached to pressure transducers inserted into the subarachnoid space through laminectomies at C3 and L4. Pressure measurements were taken when body position was inclined to 30degree, 60degree, and 90degree. A lumbar durotomy was performed to simulate the effects of lumbar subarachnoid drainage. The body was repositioned to 90degree, and pressure was measured. Results. As inclination increased from 0degree to 90degree, the mean cervical cerebrospinal fluid pressure significantly decreased. The mean lumbar subarachnoid pressure significantly increased, as inclination increased from 0degree to 90degree. Lumbar durotomy plus repositioning to 90degree resulted in a significant reduction in cervical cerebrospinal fluid subarachnoid pressure, with pressure dropping by 46%. Lumbar cerebrospinal fluid subarachnoid pressure dropped to zero after lumbar durotomy plus repositioning to 90degree. Conclusions. Cerebrospinal fluid pressures in the subarachnoid space of both the cervical and lumbar spines are affected by changes in body position. Both patient positioning and lumbar drainage may be important in reducing cervical cerebrospinal fluid pressure, and may reduce the occurrence of cerebrospinal fluid leaks after primary dural repair in the neck.

Descriptors: models and simulations, computational biology, nervous system, neural coordination, skeletal system, movement and support, dural leak, connective tissue disease, injury, dural tear, angiocatheter, laboratory equipment, cervical surgery, clinical techniques, therapeutic and prophylactic techniques, laminectomy, experimental surgical techniques, laboratory techniques, lumbar durotomy, experimental surgical techniques, pressure transducer, laboratory equipment, body position, cerebral spinal fluid pressure, in vivo model, lumbar subarachnoid drainage, postoperative complications, subarachnoid pressure.

Cooper, J.J., C. Ashton, S. Bishop, R. West, D.S. Mills, and R.J. Young (2003). **Clever hounds: social cognition in the domestic dog (canis familiaris).** *Applied Animal Behaviour Science* 81(3): 229-244. ISSN: 0168-1591.

NAL Call Number: QL750.A6

Abstract: This paper reviews the reasons why domestic dogs make good models to investigate cognitive processes related to social living and describes experimental approaches that can be adopted to investigate such processes in dogs. Domestic dogs are suitable models for investigating social cognition skills for three broad reasons. First, dogs originated from wolves, social animals that engage in a number of co-operative behaviours, such as hunting and that may have evolved cognitive abilities that help them predict and interpret the actions of other animals. Second, during domestication dogs are likely to have been selected for mental adaptations for their roles in human society such as herding or companionship. Third, domestic dogs live in a human world and "enculturation" may facilitate the development of relevant mental skills in dogs. Studies of social cognition in animals commonly use experimental paradigms originally developed for pre-verbal human infants. Preferential gaze, for example, can be used as a measure of attention or "surprise" in studies using expectancy violation. This

approach has been used to demonstrate simple numerical competence in dogs. Dogs also readily use both conspecific and human social signals (e.g. looking or pointing) as information sources to locate hidden rewards such as food or favourite toys. Such abilities make dogs particularly good models for investigating perspective-taking tasks, where animals are required to discriminate between apparently knowledgeable and apparently ignorant informants.
Descriptors: behavior, evolution and adaptation, neural coordination, attention, companionship, counting, domestication, evolution, herding, hunting, mental skills, numerical competence, preferential gaze, reward, social cognition.

Durand, D.M. (2007). **Neural engineering--a new discipline for analyzing and interacting with the nervous system.** *Methods of Information in Medicine* 46(2): 142-6. ISSN: 0026-1270.
Abstract: OBJECTIVES: The field of neural engineering focuses on an area of research at the interface between neuroscience and engineering. The area of neural engineering was first associated with the brain machine interface but is much broader and encompasses experimental, computational, and theoretical aspects of neural interfacing, neuroelectronics, neuromechanical systems, neuroinformatics, neuroimaging, neural prostheses, artificial and biological neural circuits, neural control, neural tissue regeneration, neural signal processing, neural modelling and neuro-computation. One of the goals of neural engineering is to develop a selective interface for the peripheral nervous system. METHODS: Nerve cuffs electrodes have been developed to either reshape or maintain the nerve into an elongated shape in order to increase the circumference to cross sectional ratio. It is then possible to place many electrodes around the nerve to achieve selectivity. This new cuff (flat interface nerve electrode: FINE) was applied to the hypoglossal nerve and the sciatic nerve in dogs and cats to estimate the selectivity of the interface. RESULTS: By placing many contacts close to the axons, three different types of selectivity were achieved: 1) The FINE could generate a high degree of stimulation selectivity as estimated by the individual fascicle recording. 2) Similarly, recording selectivity was also demonstrated and blind source algorithms were applied to recover the signals. 3) Finally, by placing arrays of electrodes along the nerve, small fiber diameters could be excited before large fibers thereby reversing the recruitment order. CONCLUSION: Taking advantage of the fact that nerves are not round but oblong or flat allows a novel design for selective nerve interface with the peripheral nervous system. This new design has found applications in many disorders of the nervous system such as bladder incontinence, obstructive sleep apnea and stroke.
Descriptors: central nervous system, electrodes, implanted, nerve tissue physiology, peripheral nerves physiology, prostheses and implants, signal processing, computer assisted, algorithms, dogs, hypoglossal nerve physiology, models, animal, models, biological, sciatic nerve physiology.

Furukawa, N., M. Hatano, and E. Nakamura (2003). **Antro-pancreatic reflexes: long- and short-route reflexes in exocrine and endocrine pancreatic secretion in dogs.** *Autonomic Neuroscience Basic and Clinical* 106(2): 110-118. ISSN: 1566-0702.
Abstract: Pancreatic exocrine secretion is known to be facilitated by gastric antral distension via long- and short-route reflexes. In this study, we studied the effects of gastric distension on intra-pancreatic nerve discharges and blood insulin level as well as pancreatic exocrine

secretion. Mongrel dogs were anesthetized with ketamine and thiopental, and immediately decerebrated. This study consisted of two series of experiments. In the first series, efferent discharges in an intra-pancreatic nerve branch were recorded, and its responses to antral distension were analyzed. In the second series, effects of antral distension on pancreatic exocrine secretion and blood insulin level were observed before and after vagotomy in splanchnicectomized dogs. Efferent discharges in a pancreatic nerve branch were increased by antral distension. Neither vagotomy nor splanchnicectomy produced obvious changes in the neural response. In splanchnicectomized dogs, antral distension elevated blood insulin level and increased pancreatic exocrine secretion. After subsequent vagotomy, these effects were reduced, but the increases were still greater than 50%. These results indicate that the antro-pancreatic short-route reflex plays a significant role in exocrine secretion, and also suggest that insulin release is increased by antral distension independent of blood glucose level.
Descriptors: endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, splanchnicectomy, experimental surgical techniques, laboratory techniques, vagotomy, antro pancreatic reflexes, gastric distension.

Green, S.L., J.M. Westendorf, H. Jaffe, H.C. Pant, L.C. Cork, E.A. Ostrander, F. Vignaux, and J.E.J. Ferrell (2005). **Allelic variants of the canine heavy neurofilament (NFH) subunit and extensive phosphorylation in dogs with motor neuron disease.** *Journal of Comparative Pathology* 132(1): 33-50. ISSN: 0021-9975.
NAL Call Number: 41.8 J82
Abstract: Aberrant accumulation of extensively phosphorylated heavy (high molecular weight) neurofilament (NFH) and neurodegeneration are features of hereditary canine spinal muscular atrophy (HCSMA), an animal model of human motor neuron disease. In this study, the canine NFH gene was mapped, cloned, and sequenced, and electrospray/mass spectrometry was used to evaluate the phosphorylation state of NFH protein from normal dogs and dogs with HCSMA. The canine NFH gene was localized to a region on canine chromosome 26 that corresponds to human NFH on chromosome 22q. The predicted length of the canine NFH protein is 1135 amino acids, and it shares an 80.3% identity with human NFH and >74.6% with murine NFH proteins. Direct sequencing of NFH cDNA from HCSMA dogs revealed no mutations, although cDNA sequence and restriction fragment length polymorphism (RFLP) analysis indicates that there are at least three canine NFH alleles, differing in the position and number (61 or 62) of Lys-Ser-Proline (KSP) motifs. The two longest alleles (L1 and L2), each with 62 KSP repeats, contain an additional 24-base insert and were observed in both normal and HCSMA dogs. However, the shorter allele (the C allele), with 61 KSP sites and lacking the 24-base insertion, was absent in dogs with HCSMA. Mass spectrometry data indicated that almost all of the NFH KSP phosphorylation sites were occupied. No new or extra sites were identified in native NFH purified from the HCSMA dogs. The predominance of the two longest NFH alleles and the additional KSP phosphorylation sites they confer probably account for the presence of extensively phosphorylated NFs detected immunohistochemically in dogs with HCSMA.
Descriptors: animal model, human motor neuron disease, genetics, hereditary canine spinal muscular atrophy (HCSMA), neurodegeneration .
Notes: Library: National-Library-of-Medicine.

Green, S.L., D.M. Bouley, M.J. Pinter, L.C. Cork, and G.T. Vatassery (2001). **Canine motor neuron disease: clinicopathologic features and selected indicators of oxidative stress**. *Journal of Veterinary Internal Medicine* 15(2): 112-119. ISSN: 0891-6640.

NAL Call Number: SF601.J65

Abstract: Hereditary canine spinal muscular atrophy (HCSMA) is an inherited motor neuron disease affecting a kindred of Brittanies. We have examined the clinicopathologic abnormalities in 57 animals with HCSMA, including 43 affected adult dogs and 14 homozygote pups. We also measured selected biochemical indices of oxidative stress: serum vitamin E (alpha-tocopherol) and Se concentrations; serum concentrations of Cu, Zn, Mg, and Fe; and total superoxide dismutase and glutathione peroxidase activities in red blood cells. Dogs with HCSMA had the following abnormalities: regenerative anemia, hypoglobulinemia, hypochloremia, and abnormally high creatine kinase and liver alkaline phosphatase activities. Serum Cu concentration was significantly (P = .01) increased in adult dogs with HCSMA compared to control dogs. Serum vitamin E concentrations tended to be lower in adult dogs with HCSMA compared to controls, and were significantly (P = .01) lower in homozygote pups compared to control pups.

Descriptors: veterinary medicine, medical sciences, neural coordination, hereditary canine spinal muscular atrophy, nervous system disease, motor neuron disease, muscle disease, clinicopathologic features, oxidative stress.

Harris, S.B., M.G. Darwin, S.R. Russell, J.M. O'Farrell, M. Fletcher, and B. Wowk (2001). **Rapid (0.5 degrees C/min) minimally invasive induction of hypothermia using cold perfluorochemical lung lavage in dogs.** *Resuscitation* 50(2): 189-204. ISSN: 0300-9572.

Abstract: OBJECTIVE: Demonstrate minimally invasive rapid body core and brain cooling in a large animal model. DESIGN: Prospective controlled animal trial. SETTING: Private research laboratory. SUBJECTS: Adult dogs, anesthetized, mechanically ventilated. INTERVENTIONS: Cyclic lung lavage with FC-75 perfluorochemical (PFC) was administered through a dual-lumen endotracheal system in the new technique of 'gas/liquid ventilation' (GLV). In Trial-I, lavage volume (V-lav) was 19 ml/kg, infused and withdrawn over a cycle period (tc) of 37 s. (effective lavage rate V'-lav=31 ml/kg/min.) Five dogs received cold (approximately 4 degrees C) PFC; two controls received isothermic PFC. In Trial-II, five dogs received GLV at V-lav=8.8 ml/kg, tc=16 s, V'-lav=36 ml/kg/min. MEASUREMENTS AND MAIN RESULTS: Trial-I tympanic temperature change was -3.7+/-0.6 degrees C (SD) at 7.5 min, reaching -7.3+/-0.6 degrees C at 18 min. Heat transfer efficiency was 60%. In Trial-II, efficiency fell to 40%, but heat-exchange dead space (VDtherm) remained constant. Lung/blood thermal equilibration half-time was <8 s. Isothermic GLV caused hypercapnia unless gas ventilation was increased. At necropsy after euthanasia (24 h), modest lung injury was seen. CONCLUSIONS: GLV cooling times are comparable to those for cardiopulmonary bypass. Heat and CO(2) removal can be independently controlled by changing the mix of lavage and gas ventilation. Due to VDtherm of approximately 6 ml/kg in dogs, efficient V-lav is >18 ml/kg. GLV cooling power appears more limited by PFC flows than lavage residence times. Concurrent gas ventilation may mitigate heat-diffusion limitations in liquid breathing, perhaps via bubble-induced turbulence.

Descriptors: animal model, minimally invasive, rapid body core, brain cooling, hypothermia
.

Horais, K., V. Hruby, S. Rossi, D. Cizkova, C. Meschter, R. Dorr, and T.L. Yaksh (2003). **Effects of chronic intrathecal infusion of a variant delta opioid agonist in dogs.** *Toxicological Sciences* 71(2): 263-275. ISSN: 1096-6080.

NAL Call Number: RA1190.F8

Abstract: To define the effects of chronic spinal exposure to a highly selective variant delta opioid agonist c(DPen2,DPen5)enkephalin (DPDPE), adult beagles were prepared with chronic lumbar intrathecal catheters. Groups of dogs received intrathecal infusions (100 mul/h) of saline (vehicle), DPDPE 3 mg/ml or 6 mg/ml for 28 days. Over the 28-day period, saline or 3 mg/ml showed minimal changes in neurological function, whereas in the 6 mg/ml animals, prominent hind limb dysfunction evolved over the 28-day interval. Histopathology in control animals displayed a modest pericatheter reaction considered normal for this model. Dogs receiving DPDPE (three of four at 6 mg/ml and one of four at 3 mg/ml) but not saline (zero of four) developed large inflammatory masses (granulomas) in the intrathecal space located proximal to the catheter tip. In these masses, severe chronic inflammatory changes in combination with necrosis and fibrosis was detected. Occasional focal destruction of neuropil was detected also in the adjacent spinal cord parenchyma. These masses contained extensive accumulation of mouse antihuman macrophages (MAC)-positive inflammatory cells expressing tumor necrosis factor-alpha (TNF-alpha), revealing infiltration of macrophages, granulocytes, and monocytes. In separate animals, prepared with dual intrathecal catheters, lumbar CSF was sampled at specified time points following intrathecal bolus (3 mg/ml) and 24 h DPDPE infusion (3 mg/ml and 6 mg/ml). Steady-state cerebrospinal fluid (CSF) DPDPE levels were 18.6 +- 1.0 and 22.6 +- 4.0 mug/ml for 3 mg/ml and 6 mg/ml infusions respectively. These results indicate that this variant delta opioid agonist DPDPE produces a concentration and time-dependent formation of an intrathecal inflammatory mass.

Descriptors: neural coordination, pharmacology, toxicology, hind limb dysfunction, nervous system disease, toxicity, drug induced, intrathecal granuloma.

Ito, T., T. Nakamura, K. Suzuki, T. Takagi, T. Toba, A. Hagiwara, K. Kihara, T. Miki, H. Yamagishi, and Y. Shimizu (2003). **Regeneration of hypogastric nerve using a polyglycolic acid (pga)-collagen nerve conduit filled with collagen sponge proved electrophysiologically in a canine model.** *International Journal of Artificial Organs* 26(3): 245-251. ISSN: 0391-3988.

Abstract: The hypogastric nerve (HGN) is a sympathetic nerve in the peritoneal cavity and controls urinary and seminal functions. In this study, the regeneration of HGN was determined by using a new type of an artificial nerve conduit, polyglycolic acid (PGA)-collagen nerve conduit filled with collagen sponge in two dogs. A PGA-collagen nerve conduit (diameter=2mm) was interposed in a 10 mm gap of the right HGN. The regeneration of the HGN was evaluated electrophysiologically 8 months after the operation. The intraluminal pressure of spermatic duct and the bladder neck were elevated 80 mmHg and 25 mmHg respectively by the stimulation across the regenerated HGN. The prostate contraction was also elicited. The responses diminished after the excision of the regenerated portion of HGN. These results proved the regeneration of HGN and this nerve conduit will be great help for patients who suffer from urinary and seminal disturbances.

Descriptors: nervous system, neural coordination, polyglycolic acid collagen nerve conduit, laboratory equipment.

Juraschko, K., A. Meyer Lindenberg, I. Nolte, and O. Distl (2003). **Analysis of systematic effects on congenital sensorineural deafness in german dalmatian dogs.** *Veterinary Journal* 166(2): 164-169. ISSN: 1090-0233.

NAL Call Number: SF601.V484

Abstract: We have analysed the systematic influences, phenotypic colour markers and the additive genetic variation for congenital sensorineural deafness (CSD) in German Dalmatian dogs in order to help elucidate the importance of phenotypic breed characteristics for genetic differences of CSD. Linear animal models using restricted maximum likelihood methods were employed to estimate variance components. Data were obtained from all three German Dalmatian kennel clubs associated with the German Association for Dog Breeding and Husbandry (VDH). CSD was recorded by standardized protocols for brainstem auditory-evoked response (BAER). The material included 1899 German Dalmatian dogs from 354 litters in 169 different kennels. BAER testing results were from the years 1986 to 1999. Pedigree information was available for up to seven generations. The animal model regarded the fixed effects of sex, coat colour, eye colour, presence of patches, litter size, percentage of examined puppies per litter, kennel club, and inbreeding coefficient. The common environment of the litter and kennel as well as the additive genetic effect of the animal were taken into account as randomly distributed effects. The fixed effects of eye colour, percentage of puppies examined per litter and kennel club were significant in the mixed model analysis. A significant proportion of additive genetic variation could be shown despite corrections for phenotypic colour variants. The heritability estimate for CSD in German Dalmatian dogs was h2 = 0.27 +- 0.07. The additive genetic correlation of CSD with presence of blue eyes was rg = 0.53 +- 0.41 and with presence of patches rg = -0.36 +- 0.24. We concluded that additional genes other than those associated with phenotypic colour markers in German Dalmatian dogs significantly contribute to the occurrence of CSD.

Descriptors: molecular genetics, biochemistry and molecular biophysics, nervous system, neural coordination, sense organs, sensory reception, veterinary medicine, medical sciences, congenital sensorineural deafness, CSD, congenital disease, ear disease, nervous system disease, diagnosis, genetics, therapy, german association for dog breeding and animal husbandry, brainstem auditory evoked response, breeding, genetic variation, phenotypic color markers.

Kakiuchi, M., T. Ohashi, K. Tanaka, N. Ohara, K. Kamiyama, K. Morikawa, and H. Kato (1998). **Central nervous system effects of the novel antiallergic agent hsr-609 and typical antiallergic agents using behavioral and electroencephalographic analyses in dogs**. *Japanese Journal of Psychopharmacology* 18(5): 189-199. ISSN: 1340-2544.

Abstract: We studied the central nervous system (CNS) effects of 3-(4-(8-fluoro-5, 11-dihydrobenz(b) oxepino(4, 3-b)pyridin-11-ylidene)piperidino)propionic acid dihydrate (HSR-609), a novel amphoteric antiallergic agent having antihistaminic activity. Its effects on gross behavior, spontaneous electroencephalograms (EEG) and some pharmacological parameters of unanesthetized, unrestrained dogs with chronic indwelling brain electrodes after oral administration were compared with typical antiallergic agents and 8-fluoro-5, 11-dihydro-11-(1-methyl-4-piperidylidene)benz(b)oxepino(4,3-b)pyridine (PY-608), a non-amphoteric basic compound having a similar chemical structure to HSR-609. HSR-609 (1, 10 and 100 mg/kg) and terfenadine (100 mg/kg) had no effect on the behavior, EEG patterns, sleep-

wakefulness cycles or EEG power spectrum. Cyproheptadine (10 mg/kg), ketotifen (30 mg/kg) and PY-608 (10 mg/kg) increased slow waves with high amplitude in all EEG leads and caused dissociation between the slowing of EEG and waking behavior. Both azelastine (30 mg/kg) and oxatomide (100 mg/kg) caused generalized seizure discharges accompanied by agitation with the former and sedation with the latter. These findings suggest that observations of behavior and EEG in conscious dogs can be useful for clarifying the pharmacological characteristics of various antiallergic agents on the CNS. We were able to show that HSR-609 has no effect on the behavior and EEG of dogs because of its amphoteric chemical structure.
Descriptors: behavior, nervous system, neural coordination, pharmacology, electroencephalography, monitoring method.

Kakkis, E., M. Passage, P. Belichenko, M. Mcentee, C. Le S Vogler, R. Esquivel, and W. Mobley (2003). **Effective reduction of lysosomal storage in brain and meninges following intrathecal administration of iduronidase in canine mucopolysaccharidosis i (mps i).** *Journal of Inherited Metabolic Disease* 26(Supplement 2): 141. ISSN: 0141-8955.
NAL Call Number: RC627.8.J68
Descriptors: metabolism, nervous system, neural coordination, canine mucopolysaccharidosis I, connective tissue disease, genetic disease, metabolic disease, therapy, enzyme replacement therapy, clinical techniques, therapeutic and prophylactic techniques

Kaluzienski, M. (2000). **Partial paralysis and altered behavior in dogs treated with melaleuca oil**. *Journal of Toxicology Clinical Toxicology* 38(5): 518-519. ISSN: 0731-3810.
NAL Call Number: RA1190.C5
Descriptors: biochemistry and molecular biophysics, veterinary medicine, medical sciences, toxicology, altered behavior, partial paralysis, meeting abstract

Kangasniemi, M., R.J. Stafford, R.E. Price, E.F. Jackson, and J.D. Hazle (2003). **Dynamic gadolinium uptake in thermally treated canine brain tissue and experimental cerebral tumors.** *Investigative Radiology* 38(2): 102-107. ISSN: 0020-9996.
Abstract: RATIONALE AND OBJECTIVES: Thermal coagulation of cerebral tumors induces reactive changes within adjacent brain tissue, which appear as Gd-DTPA enhancement in MR images. This makes assessment of therapeutic success difficult to establish radiographically because the reactive changes can mimic residual tumor. Dynamic Gd-DTPA uptake curves in reactive tissue and tumor were investigated to assess the utility of contrast enhanced (CE)-dynamic MRI to distinguish reactive changes from residual tumor in a canine model. MATERIALS AND METHODS: Cerebral thermal necrosis was induced using a 980 nm laser in 11 dogs with intracerebral transmissible venereal tumors (TVTs). A fast spin-echo T1-weighted imaging sequence was used for CE-dynamic MRI. Gd-DTPA uptake data were acquired with 10-second temporal resolution and for untreated TVTs for reactive tissue using a sigmoidal-exponential model. RESULTS: Characteristic gadolinium uptake curves were measured and characterized for reactive brain tissue, and untreated and treated TVTs. Both early and delayed dynamic responses were significantly different in reactive brain tissue compared with TVT. CONCLUSION: Reactive thermal changes in otherwise normal brain tissue can be distinguished from residual tumor after cerebral thermal

therapy using CE -dynamic MRI.
Descriptors: nervous system, neural coordination, pharmacology, tumor biology, cerebral thermal necrosis, nervous system disease, intracerebral transmissible venereal tumor, neoplastic disease, radiotherapy, contrast enhanced dynamic magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, fast spin echo t1 weighted imaging, sigmoidal exponential model, mathematical and computer techniques, thermal coagulation therapy, therapeutic and prophylactic techniques, reactive thermal change.

Lamouche, S. and N. Yamaguchi (2003). **Pacap release from the canine adrenal gland in vivo: its functional role in severe hypotension.** *American Journal of Physiology* 284(2 Part 2): R588-R597. ISSN: 0002-9513.
NAL Call Number: 447.8 Am3
Abstract: This study was to investigate if endogenous pituitary adenylate cyclase-activating polypeptide (PACAP) can be released during direct splanchnic nerve stimulation in vivo and to determine whether PACAP in the adrenal gland can modulate the medullary response to sympathoadrenal reflex. The output of adrenal catecholamine and PACAP-38-like immunoreactivity (PACAP-38-ir) increased in a frequency-dependent manner after direct splanchnic nerve stimulation (0.2-20 Hz). Both responses were highly reproducible, and PACAP-38-ir output closely correlated with catecholamine output. Sodium nitroprusside (SNP; 0.1 mg/kg iv bolus) caused a severe hypotension resulting in marked increases in catecholamine secretion. In the presence of local PACAP-27 (125 ng), the maximum catecholamine response to SNP was significantly potentiated in a synergistic manner compared with that obtained in the group receiving SNP or PACAP-27 alone. The study indicates that endogenous PACAP-38 can be released particularly when the sympathoadrenal system is highly activated and that the local exogenous PACAP-27 enhanced the reflex-induced catecholamine release, suggesting collectively a facilitating role of PACAP as neuromodulator in the sympathoadrenal function in vivo.
Descriptors: endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, hypotension,vascular disease, sympathoadrenal reflex.

Leonard, S.E. and R. Kirby (2002). **The role of glutamate, calcium and magnesium in secondary brain injury**. *Journal of Veterinary Emergency and Critical Care* 12(1): 17-32. ISSN: 1534-6935.
NAL Call Number: SF778.J68
Abstract: Objective: To review the roles that glutamate, calcium and magnesium play in both normal brain function and in the events following traumatic brain injury. Human data synthesis: Elevated extracellular brain glutamate levels have been well documented in humans following traumatic brain injury. Therapies focusing on glutamate receptor antagonists have not yet been shown to have clinical effectiveness significant enough to outweigh the side effects. Newer strategies are currently being explored focusing on the many secondary cellular cascades interacting to culminate in cell injury and death. Veterinary data synthesis: Derangements in glutamate, calcium and magnesium have been well documented in animals following traumatic brain injury. Research studies using animal models other than small laboratory animals such as rats, mice and rabbits are very limited. Prospective veterinary clinical

trials in dogs and cats are needed to determine the potential success that various therapeutic strategies might have in the field of small animal emergency and critical care medicine. Conclusions: Alterations in the levels of glutamate, calcium and magnesium play a critical role in secondary brain injury. The future development of clinically-tolerated and effective antagonists of glutamate, glutamate receptors, and other downstream mediators has the potential to revolutionize the therapy of traumatic brain injured patients.
Descriptors: animal health, brain, calcium, glutamates, glutamic acid, intensive care, magnesium, therapy, trauma, cats, dogs.

Lian, X.Y. and J.L. Stringer (2004). **Inhibition of aconitase in astrocytes increases the sensitivity to chemical convulsants**. *Epilepsy Research* 60(1): 41-52. ISSN: 0920-1211.
Descriptors: behavior, nervous system, neural coordination, pharmacology, epilepsy, nervous system disease, neuronal damage, injury, nervous system disease, seizure, wet dog shakes, nervous system disease, drug induced, etiology, pathology, immunohistochemistry, immunologic techniques, laboratory techniques, silver staining, genetic techniques, chemical convulsant sensitivity.

Macdonald, R.L., L.S. Marton, P.K. Andrus, E.D. Hall, L. Johns, and M. Sajdak (2004). **Time course of production of hydroxyl free radical after subarachnoid hemorrhage in dogs**. *Life Sciences* 75(8): 979-989. ISSN: 0024-3205.
NAL Call Number: Q2.C6
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, nervous system, neural coordination, subarachnoid hemorrhage, nervous system disease, vascular disease, vasospasm, lipid peroxidation.

Mealey, K.L., S. Greene, R. Bagley, J. Gay, R. Tucker, P. Gavin, K. Schmidt, and F. Nelson (2008). **P-glycoprotein contributes to the blood-brain, but not blood-cerebrospinal fluid, barrier in a spontaneous canine p-glycoprotein knockout model.** *Drug Metabolism and Disposition the Biological Fate of Chemicals* 36(6): 1073-9.
NAL Call Number: RM300.A1D7
Abstract: P-glycoprotein is considered to be a major factor impeding effective drug therapy for many diseases of the central nervous system (CNS). Thus, efforts are being made to gain a better understanding of P-glycoprotein's role in drug distribution to brain parenchyma and cerebrospinal fluid (CSF). The goal of this study was to validate and introduce a novel P-glycoprotein-deficient (ABCB1-1Delta) canine model for studying P-glycoprotein-mediated effects of drug distribution to brain tissue and CSF. CSF concentrations of drug are often used to correlate efficacy of CNS drug therapy as a surrogate for determining drug concentration in brain tissue. A secondary goal of this study was to investigate the validity of using CSF concentrations of P-glycoprotein substrates to predict brain tissue concentrations. Loperamide, an opioid that is excluded from the brain by P-glycoprotein, was used to confirm a P-glycoprotein-null phenotype in the dog model. ABCB1-1Delta dogs experienced CNS depression following loperamide administration, whereas ABCB1 wild-type dogs experienced no CNS depression. In summary, we have validated a novel P-glycoprotein-deficient canine model and have used the model to investigate transport of the P-glycoprotein substrate (99m)Tc-sestamibi at the blood-brain barrier and blood-CSF barrier.

Descriptors: blood brain barrier metabolism, central nervous system depressants pharmacology, loperamide pharmacology, models, animal, p glycoprotein genetics, technetium tc 99m sestamibi cerebrospinal fluid, brain metabolism, dogs, technetium tc 99m sestamibi pharmacokinetics.

Miklosi, A., J. Topal, and V. Csanyi (2007). **Big thoughts in small brains? Dogs as a model for understanding human social cognition.** *Neuroreport* 18(5): 467-71. ISSN: 0959-4965.
Abstract: In this review we argued that dogs can provide a good model for both the evolution of human social-cognitive abilities and studying the underlying neural and genetic structures of these behavioural features. The key difference between the present and other approaches for modelling human social evolution lies in the assumption that there is a large overlap between the human and dog behaviour complex because during their evolution in close contact with human groups dogs evolved functionally similar social skills. Thus the parallel investigation of the human and dog behaviour complex widens our possibility for understanding human social cognition because it allows the modelling of the interaction between various components in contrast to other models which are often restricted to modelling a single aspect of human social cognitive skills.
Descriptors: brain physiology, cognition physiology, evolution, social behavior, brain anatomy and histology, dogs, models, animal.

Milgram, N.W. (2003). **Cognitive experience and its effect on age dependent cognitive decline in beagle dogs**. *Neurochemical Research* 28(11): 1677-1682. ISSN: 0364-3190.
NAL Call Number: QP356.3 .N457
Abstract: Test-sophisticated beagle dogs show marked age sensitivity in a size discrimination learning task, with old and senior dogs performing significantly more poorly than young dogs. By contrast, age differences in learning were not seen in dogs naive with respect to neuropsychological test experience. These results indicate that old animals benefit less from prior cognitive experience than young animals, which is an example of an age-dependent loss in plasticity. This finding also suggests that behaviorally experienced animals are a more useful model of human cognitive aging than behaviorally naive animals. We also looked at the effect of a program of behavioral enrichment in aged dogs. One year of enrichment did not lead to significant differences, but after 2 years the behaviorally enriched group performed significantly better than the control group. The effect after 2 years indicates that a prolonged program of cognitive enrichment can serve as an effective intervention in aged dogs. These findings demonstrate that cognitive abilities in aged animals can be modified by providing behavioral experience, indicating that cognitive abilities remain moderately plastic, even in very old animals.
Descriptors: beagle, breed, age effects,cognition,neuropsychological tests,age-dependedn loss in plasticity,behavioral enrichment, length of enrichment program.

Monaco, B.A., A. Benicio, I.S. Contreras, L.E. Mingrone, G. Ballester, and L.F. Moreira (2007). **Ischemic preconditioning and spinal cord function monitoring in the descending thoracic aorta approach.** *Arquivos Brasileiros De Cardiologia* 88(3): 291-6.
NAL Call Number: RC681.A1
Abstract: OBJECTIVES: To evaluate the effectiveness of acute ischemic preconditioning

(IP), based on somatosensory evoked potentials (SSEP) monitoring, as a method of spinal cord protection and to asses SSEP importance in spinal cord neuromonitoring. METHODS: Twenty-eight dogs were submitted to spinal cord ischemic injury attained by descending thoracic aorta cross-clamping. In the C45 group, the aortic cross-clamping time was 45 min (n=7); in the IP45 group, the dogs were submitted to IP before the aortic cross-clamping for 45 min (n=7). In the C60 group, the dogs were submitted to 60 min of aortic cross-clamping (n=7), as in the IP60 group that was previously submitted to IP. The IP cycles were determined based on SSEP changes. RESULTS: Tarlov scores of the IP groups were significantly better than those of the controls (p = 0.005). Paraplegia was observed in 3 dogs from C45 and in 6 from C60 group, although all dogs from IP45 group were neurologically normal, as 4 dogs from IP60. There was a significant correlation between SSEP recovery time until one hour of aortic reperfusion and the neurological status (p = 0.011), showing sensitivity of 75% and specificity of 83%. CONCLUSION: Repetitive acute IP based on SSEP is a protection factor during spinal cord ischemia, decreasing paraplegia incidence. SSEP monitoring seems to be a good neurological injury assessment method during surgical procedures that involve spinal cord ischemia.

Descriptors: aorta, thoracic surgery, evoked potentials, somatosensory physiology, ischemic preconditioning standards, spinal cord ischemia diagnosis, spinal cord ischemia prevention and control, analysis of variance, dogs, ischemic preconditioning methods, models, animal, monitoring, intraoperative methods, paraplegia etiology, reperfusion methods, sensitivity and specificity, spinal cord blood supply, spinal cord physiopathology, spinal cord ischemia etiology, spinal cord ischemia physiopathology, statistics, nonparametric, time factors, vascular surgical procedures adverse effects.

Language of Text: ; Portuguese; Non-.

Naito, M., X.P. Yang, and S. Chiba (2004). **Modification of transmitter release from periarterial nerve terminals by dipyridamole in canine isolated splenic artery.** *Clinical and Experimental Pharmacology and Physiology* 31(3): 185-189. ISSN: 0305-1870.

Abstract: 1. The aim of the present study was to determine the modulatory effects of dipyridamole on purinergic and adrenergic transmission in the canine isolated, perfused splenic artery. 2. Periarterial nerve electrical stimulation readily induced a double-peaked vasoconstriction consisting of an initial transient, predominantly P2X receptor-mediated constriction followed by a prolonged, mainly alpha1-adrenoceptor-mediated response. 3. Exposure of tissues to dipyridamole (0.1-1 mumol/L) dose-dependently inhibited both the first and second peaks of the vasoconstrictor response at a low frequency of stimulation (1 Hz), whereas at an intermediate frequency of stimulation (4 Hz), the first peak of the response was depressed without any significant effect being observed on the second peak of constriction. 4. At a higher dose (1 mumol/L) dipyridamole potentiated vasoconstrictor responses to noradrenaline (0.03-1 nmol). At any doses used, dipyridamole had no effect on the vasoconstrictor responses to ATP (0.03-1 mumol). 5. Tyramine (0.01-0.3 mumol) induced vasoconstriction in a dose-dependent manner. The dose-response curves for tyramine were shifted to the right following treatment with dipyridamole (0.1-1 mumol/L). 6. The present results indicate that dipyridamole may inhibit purinegic and adrenergic transmission presynaptically, whereas postsynaptically dipyridamole may potentiate the adrenergic vascular constriction by inhibition of transmitter uptake.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, cotransmission, neuronal vasoconstrictor response, transmitter release modification.

Nolan, E.R., M.B. Bailie, and N.B. Olivier (2008). **Effect of autonomic blockade on ventricular repolarization shortening: response to behavioral stimulus in paced dogs.** *Autonomic Neuroscience Basic and Clinical* 140(1-2): 66-71. ISSN: 1566-0702.

Abstract: Autonomic tone has been suggested to be a significant determinant of ventricular repolarization duration with both rate dependent and independent effects. Using the His bundle-paced dog, a model that eliminates the need for QT correction factors, we explored the rate-independent effects of sympathetic and parasympathetic blockade on ventricular repolarization shortening following an excitatory stimulus. Six male His bundle-paced beagle dogs were paced at 80 bpm and fitted with jackets, surface ECG electrodes, and radiotelemeters. Dogs were given propranolol, atropine methyl nitrate, or the appropriate control in a four-period crossover design. Doses were based on literature reviews and unpublished pharmacokinetic/pharmacodynamic modeling to provide efficacious beta- and parasympathetic blockade throughout the data collection period. Data collection began at 11 am and concluded at 11 am the following day, with event stimuli provided by investigators entering the room at 5 pm and at 7 am the following morning. One minute of ECG data were sampled every 15 min and these means were averaged to generate hourly means for the 24 hour data collection period. Treatment with atropine attenuated RT interval shortening when compared with the vehicle group at both the 5 pm and 7 am stimulus. In contrast, propranolol was not associated with significant effects on RT interval duration at either time point. These results suggest that parasympathetic withdrawal is the primary factor responsible during both awake hours (5 pm) and in the transition from deep sleep to the awake state (7 am) in the facilitation of RT interval shortening following an excitatory stimulus. The attenuation of RT interval shortening following atropine treatment may be a direct effect, or an indirect effect requiring an excited state to become evident. The use of a model that eliminates the need to apply correction factors to repolarization indices helps to clarify the role of the autonomic nervous system on ventricular repolarization.

Descriptors: autonomic nervous system physiology, heart innervation, heart physiology, heart rate physiology, heart ventricles innervation, ventricular function, adrenergic beta antagonists pharmacology, atropine pharmacology, autonomic nervous system drug effects, biological clocks drug effects, biological clocks physiology, bundle of his drug effects, bundle of his physiology, circadian rhythm physiology, dogs, electric stimulation, electrocardiography drug effects, heart rate drug effects, membrane potentials drug effects, membrane potentials physiology, models, animal, muscarinic antagonists pharmacology, pacemaker, artificial, parasympathetic nervous system drug effects, parasympathetic nervous system physiology, propranolol pharmacology, sympathetic nervous system drug effects, sympathetic nervous system physiology, time factors.

Qureshi, A.I., M.F. Suri, A.J. Ringer, L.R. Guterman, and L.N. Hopkins (2002). **Regional intraparenchymal pressure differences in experimental intracerebral hemorrhage: effect of hypertonic saline.** *Critical Care Medicine.* 30(2): 435-41. ISSN: 0090-3493.

Abstract: OBJECTIVE: To study regional intraparenchymal pressures within the cranial cavity during and after formation of intracerebral hemorrhage. We also assessed the effect

of hypertonic saline on intraparenchymal pressure in different brain regions and on regional brain distribution of sodium within the brain. DESIGN: Prospective, controlled, laboratory trial. SETTINGS: Animal research laboratory. SUBJECTS: Eight mongrel dogs, weighing 15-25 kg. INTERVENTION: We introduced an intracerebral hematoma in eight mongrel dogs by infusing 6 mL of autologous arterial blood in the deep white matter adjacent to the basal ganglia. Sodium chloride (23.4%, 1.4 mL/kg) then was administered intravenously 6 hrs after introduction of hematoma. MEASUREMENTS AND MAIN RESULTS: Parenchymal pressure monitors were placed in the perihematoma region, both frontal lobes, and the cerebellum to record intraparenchymal pressure during and 6 hrs after intracerebral hematoma formation. Intraparenchymal pressure measurements were recorded for 3 more hours after administration of 23.4% sodium chloride. Regional cerebral perfusion pressure was calculated for each intraparenchymal pressure measurement. Regional sodium distribution was measured in extracts from brain regions by using ion selective electrode technique. A higher elevation in intraparenchymal pressure was recorded in the perihematoma region during the introduction of the hematoma compared with other compartments. After 5 mL of autologous blood was introduced, intraparenchymal pressure (mm Hg +/- SE) was significantly higher in the perihematoma region (42.1 +/- 3.5) than in the ipsilateral (30.0 +/- 4.6, $p < .05$) and contralateral (27.1 +/- 5.5, $p < .01$) frontal lobes and cerebellum (29.1 +/- 4.5, $p < .05$). Four hours after introduction of the hematoma, the cerebral perfusion pressure recorded in the perihematoma region (43.6 +/- 9.7) remained significantly lower than in the ipsilateral (58.6 +/- 9.3, $p < .05$) but not the contralateral frontal lobes (54.7 +/- 10.1) and cerebellum (51.0 +/- 11.1). Administration of 23.4% sodium chloride immediately reduced intraparenchymal pressure in each compartment. This effect was still observed at 3 hrs in each compartment. Sodium concentration was higher in the perihematoma region than in the frontal lobes, cerebellum, or brain stem. CONCLUSIONS: Prominent differences were observed in intraparenchymal pressure and cerebral perfusion pressure in the perihematoma region and frontal lobes during and after intracerebral hematoma. We speculate that the potential importance of regional intraparenchymal pressure differences in the clinical settings may be under appreciated. In this canine model of intracerebral hematoma, a single dose of hypertonic saline effectively reduces the intraparenchymal pressure in all regions of the brain.
Descriptors: animal model, mongrel dogs, regional intraparenchymal pressure, intracerebral hemorrhage, hypertonic saline.

Ridgway, P., T.E. Nixon, and J.P. Leach (2003). **Occupational exposure to organic solvents and long-term nervous system damage detectable by brain imaging, neurophysiology or histopathology.** *Food and Chemical Toxicology* 41(2): 153-187. ISSN: 0278-6915.
NAL Call Number: 391.8 F73
Abstract: The purpose of the present review is to assess the evidence published in scientific literature that industrial organic solvents as a generic group have the ability to induce long-term nervous system damage in workers that can be detected by techniques other than neuropsychological testing. The main body of evidence considered in this review was 40 studies involving the use of brain imaging, neurophysiological testing, gross autopsy or histopathology in groups of workers with long-term solvent exposure. Case reports involving both solvent abuse and occupational exposure, and experimental animal data have also been reviewed as supporting data. A number of the studies in groups of workers provide

evidence of the presence of marginal atrophic abnormalities in the brain or deficits in nerve conduction velocity in solvent-exposed workers. However, there are limitations in the design of many of these studies, the strength of association between exposure and effect is not consistently strong, no dose-response relationship can be detected, the reported changes lack specificity and there is no coherence between the human and experimental animal data. Overall, it is not possible to draw reliable conclusions with respect to the presence or absence of nervous system damage related to the common properties of organic solvents.
Descriptors: nervous system, neural coordination, toxicology, organic solvent abuse, brain imaging, imaging, microscopy techniques, laboratory techniques, gross autopsy, histopathology, cytology techniques .

Rozman, J. and S. Ribaric (2007). **Selective recording of electroneurograms from the left vagus nerve of a dog during stimulation of cardiovascular or respiratory systems.** *Chinese Journal of Physiology* 50(5): 240-50. ISSN: 0304-4920.
Abstract: Selective electroneurograms (ENGs) from superficial regions of the left vagus nerve of a dog were recorded with a 33-electrode spiral cuff (cuff) implanted on the nerve at the neck in an adult Beagle dog. The electrodes in the cuff were arranged in thirteen groups of three electrodes (GTE 1-13). To identify the relative positions of the particular nerve regions that innervated the heart and lungs, stimulating pulses (2 mA, 200 micros, 20 Hz) were individually delivered to all thirteen GTEs. It was shown that by delivering stimulating pulses to GTEs 4 and 9, heart rate, blood pressure and respiratory rate were modulated. Precisely, only when the stimuli were delivered to GTE 9, the heart rate began to fall and only when the stimuli were delivered to GTE 4 the rate of breathing decreased. To test the selectivity of recording the above-defined groups GTEs 4 and 9 and randomly chosen GTEs 1 and 7 were simultaneously used as recording GTEs while cardio-vascular or respiratory systems were stimulated by carotid artery compression, epinephrine injection and non-invasive, positive end-pressure ventilation. Results showed that stimulations elicited site-specific changes in ENG power spectra recorded from the superficial regions of the vagus nerve. Power spectrum of the ENG recorded with GTE 9, contained frequencies belonging to the neural activity elicited by compression of the carotid artery and injection of epinephrine. The power spectrum of the ENG recorded with GTE 4, contained frequencies belonging to the neural activity elicited by non-invasive, positive end-expiratory pressure ventilation. We concluded that the multi-electrode nerve cuff enables selective stimulation and recording of nerve activity from internal organs.
Descriptors: cardiovascular system drug effects, electrodiagnosis instrumentation, electrodiagnosis methods, respiratory system drug effects, vagus nerve physiology, blood pressure drug effects, dogs, electric impedance, electric stimulation, electrodes, electrophysiology, epinephrine pharmacology, heart rate drug effects, models, animal, sensitivity and specificity, vagus nerve anatomy and histology.

Schaefer, G.J., D.T. Kirkpatrick, J.F. Holson, C.P. Chengelis, K.S. Regan, and V.J. Piccirillo (2003). **A six-week inhalation neurotoxicity study of methyl bromide in dogs.** *Toxicological Sciences* 72(S-1): 304 ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Descriptors: nervous system, neural coordination, toxicology, locomotor activity.

Sharifov, O.F., V.V. Fedorov, G.G. Beloshapko, A.V. Glukhov, A.V. Yushmanova, and L.V. Rosenshtraukh (2004). **Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs.** *Journal of the American College of Cardiology* 43(3): 483-490. ISSN: 0735-1097.

NAL Call Number: RC681.A1

Abstract: OBJECTIVES We studied the effects of beta-adrenergic and cholinergic stimulation and blockade on spontaneous atrial fibrillation (AF) in the intact dog heart. BACKGROUND Paroxysmal AF is often preceded by changes in autonomic tone, but the relative roles of adrenergic and cholinergic influences on AF induction are not well known. METHODS Perfusion of catecholamines and acetylcholine (ACh), as well as their combination, through the sinus node artery was used to induce AF in 20 anesthetized open-chest dogs without electrical stimulation of atria. RESULTS Isoproterenol and adrenaline (10 to 100 mumol/l) induced AF in 21% (3 of 14) and 17% (1 of 6) of dogs, respectively. Atropine (1 to 2 mg) treatment prevented catecholamine-mediated AF, indicating a critical role of cholinergic tone in these AF episodes. Acetylcholine (2.8 +- 0.3 mumol/l) induced AF in all dogs. Beta-blockade by propranolol (1 mg/kg) did not prevent ACh-induced AF, but increased the threshold ACh concentration for AF induction to 23.5 +- 3.4 mumol/l ($p < 0.05$). Acetylcholine-mediated AF was facilitated by isoproterenol (1 to 2 and 10 mumol/l), which decreased the threshold ACh concentration for AF induction to 0.5 +- 0.1 and 0.4 +- 0.1 mumol/l, respectively ($p < 0.05$) and increased the AF duration (from 25 +- 7 to 141 +- 54 and 233 +- 60 s, respectively; $p < 0.05$). Epicardial mapping of the right atrium (112 unipolar electrodes) demonstrated similar activation patterns during arrhythmias induced by ACh and catecholamines. CONCLUSIONS These data indicate that although both autonomic systems play a role in AF, cholinergic stimulation is likely the main factor for spontaneous AF initiation in this animal model. Adrenergic tone modulates the initiation and maintenance of cholinergically mediated AF.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology, spontaneous atrial fibrillation, heart disease, adrenergic stimulation, cholinergic stimulation.

Shelton, G.D., M. Podell, L. Poncelet, S. Schatzberg, E. Patterson, H.C. Powell, and A.P. Mizisin (2003). **Inherited polyneuropathy in leonberger dogs: a mixed or intermediate form of charcot-marie-tooth disease?** *Muscle and Nerve* 27(4): 471-477. ISSN: 0148-639X.

Abstract: A spontaneous distal, symmetrical polyneuropathy in related Leonberger dogs with onset between 1 to 9 years of age was characterized clinically, electrophysiologically, histologically, and morphometrically. Exercise intolerance and weakness was associated with a high-steppage pelvic-limb gait, a loss or change in the pitch of the bark, and dyspnea. Neurological examination revealed marked atrophy of the distal limb muscles, depressed spinal and cranial nerve reflexes, and weak or absent movement of the laryngeal and pharyngeal muscles. Electrophysiological evaluation was consistent with denervation and was characterized by loss or marked attenuation of compound muscle action potentials and slowed motor nerve conduction velocity. Muscle biopsy specimens showed neurogenic atrophy. Chronic nerve fiber loss associated with decreased myelinated fiber density and a shift of the axonal size-frequency distribution toward smaller fibers was the predominant finding in peripheral nerve specimens. Pedigree analysis of a large multigenerational family, including nine sibships

with at least one affected individual, suggested X-linked inheritance. Mutational and linkage analysis of this family may aid in identification of the chromosomal loci and gene responsible for this inherited axonal neuropathy. Further characterization of this inherited axonal neuropathy may establish the Leonberger dog as a spontaneous animal model of inherited axonal neuropathy and possibly lead to the discovery of a new gene or genes associated with axonal variants.

Descriptors: molecular genetics, biochemistry and molecular biophysics, nervous system, neural coordination, Charcot Marie tooth disease, congenital disease, genetic disease, muscle disease, nervous system disease, chronic nerve fiber loss, distal limb muscle atrophy, dyspnea, respiratory system disease, exercise intolerance, inherited polyneuropathy, genetic disease, muscle weakness, neurogenic atrophy, cranial nerve reflex, motor nerve conduction velocity, myelinated fiber density, spinal nerve reflex.

Siwak, C.T., P. Gruet, F. Woehrle, B.A. Muggenburg, H.L. Murphey, and N.W. Milgram (2000). **Comparison of the effects of adrafinil, propentofylline, and nicergoline on behavior in aged dogs.** *American Journal of Veterinary Research* 61(11): 1410-1414. ISSN: 0002-9645.

NAL Call Number: 41.8 Am3A

Descriptors: dogs, age differences, animal behavior, efficacy, mental disorders, drug therapy, quality of life, movement, dosage, pharmacodynamics.

Notes: Includes references.

Siwak, C.T., P.D. Tapp, H.J. Lee, and N.W. Milgram (2000). **Age-associated changes in noncognitive behaviors in a canine model of aging**. *Society for Neuroscience Abstracts* 26(1-2): Abstract No. 873.3. ISSN: 0190-5295.

NAL Call Number: QP351.S6

Abstract: Locomotor activity and exploration, which depend on the brain's motor system, are typically viewed independently from cognition. While this may be justified in the case of locomotion, exploration involves sensory processing, investigation, responding to novel stimuli, and information gathering - all of which depend on cognitive processes. To better understand cognitive changes associated with aging, we have developed a number of spontaneous behavior tests, including tests of exploration. Our curiosity test consists of placing a number of novel objects in the test arena and allowing the dog to explore the objects. In this test young dogs show significantly more exploration and contact with novel objects than old dogs. In the model dog test, dogs are placed in an arena with a life-size plastic dog. Young dogs again show significantly more investigative sniffing than old dogs. Young dogs spend significantly more time in contact with a human sitting in the middle of the arena than old dogs. These tests can also distinguish cognitively impaired aged dogs from successful agers. Compared to successful agers, age-impaired dogs spend less time interacting with novel objects, less time interacting with humans, and more time reacting to their reflection in a mirror. These results indicate that aging can affect curiosity, exploration and responses to novelty rather than locomotor activity per se.

Descriptors: aging, nervous system, neural coordination, arena, laboratory equipment, behavior test, analytical method, life size plastic dog, equipment, model dog test, analytical method, age associated changes noncognitive behavior changes, investigative sniffing, mirror, meeting abstract

Siwak, C.T., P. Gruet, F. Woehrle, B.A. Muggenburg, H.L. Murphey, and N.W. Milgram (2000). **Comparison of the effects of adrafinil, propentofylline, and nicergoline on behavior in aged dogs**. *American Journal of Veterinary Research* 61(11): 1410-1414. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Abstract: Objective-To compare the efficacy of adrafinil, propentofylline, and nicergoline for enhancing behavior of aged dogs. Animals-36 Beagles between 9 and 16 years old. Procedure-Dogs were randomly assigned to receive adrafinil (20 mg/kg of body weight, PO, q 24 h; n = 12), propentofylline (5 mg/kg, PO, q 12 h; 12), or nicergoline (0.5 mg/kg, PO, q 24 h; 12) for 33 days. Baseline behaviors in an open field and in kennels (home cage) were recorded before treatment. After treatment, behaviors in the open field were recorded 2 hours after drug administration on days 2, 15, and 28, and 10 hours after administration on days 7, 20, and 33. Behaviors in the home cage were recorded 2 and 7 hours after drug administration on days 4, 17, and 30. Results-Treatment with adrafinil resulted in a significant increase in locomotion in each of the open-field tests and an increase in locomotion in the home cage. This latter increase was smaller and more variable than that in the open field. Locomotion was not affected by treatment with propentofylline or nicergoline. In the open field, sniffing decreased over time in all 3 groups, but the largest decline was observed in the propentofylline group. Conclusions and Clinical Relevance-Treatment with adrafinil may improve the quality of life of aged dogs by increasing exploratory behavior and alertness.
Descriptors: behavior, veterinary medicine, medical sciences, nervous system, neural coordination, pharmacology, alertness, exploratory behavior, locomotion, quality of life.

Siwak, C.T., P.D. Tapp, and N.W. Milgram (2001). **Effect of age and level of cognitive function on spontaneous and exploratory behaviors in the beagle dog**. *Learning and Memory* 8(6): 317-325. ISSN: 1072-0502.
Abstract: Cognitively characterized young and aged beagle dogs were administered six different spontaneous behavior tests, which provided measures of locomotion, exploration, and social interaction. Consistent with our previous findings, we obtained no overall effect of age on locomotion. We did find, however, that for the aged dogs locomotion correlated with level of cognitive function, being lowest in age-unimpaired dogs and highest in impaired dogs. Exploratory behavior, as measured by response to novelty, varied with age, with young dogs scoring the highest. Young dogs spent more time with novel toys and a person, responded more to a silhouette of a dog, and interacted more with a model dog compared to aged dogs. Among the aged dogs, age-unimpaired dogs spent the greatest amount of time sitting or standing beside a person whereas age-impaired dogs spent the most time reacting to a reflection in a mirror. The age-impaired dogs show undirected, stereotypical types of behavioral patterns. These differences in activity patterns may be linked to underlying age-associated neuropathology.
Descriptors: aging, behavior, nervous system, neural coordination, spontaneous behavior test, assessment method, experimental method, age effects, age associated neuropathology, cognitive function, level, exploration, exploratory behavior, locomotion, social interaction, spontaneous behavior.

Siwak, C.T., P.D. Tapp, S.C. Zicker, H.L. Murphey, B.A. Muggenburg, E. Head, C.W. Cotman, and N.W. Milgram (2003). **Locomotor activity rhythms in dogs vary with age and cognitive status.** *Behavioral Neuroscience* 117(4): 813-824. ISSN: 0735-7044.

NAL Call Number: QP351.B45

Abstract: Beagle dogs exhibited diurnal patterns of locomotor activity that varied as a function of age, cognitive status, and housing environment. Aged dogs housed in an indoor facility showed a delayed onset of activity following lights on and displayed shorter bouts of activity, with more rest periods during the day, compared with young dogs. Cognitively impaired aged dogs were more active and showed a delayed peak of activity compared with unimpaired aged dogs. Housing in continuous light did not disrupt activity rhythms. The effect of age was less prominent in dogs housed in an indoor/outdoor facility. This suggests that bright sunlight and natural light-dark transitions are better able to consolidate and synchronize the activity rhythms of the dogs.

Descriptors: behavior, biosynchronization, nervous system, neural coordination, locomotor activity, age related rhythm variation, cognitive status related rhythm variation, diurnal rhythms.

Swissa, M., S. Zhou, I. Gonzalez Gomez, C.M. Chang, A.C. Lai, A.W. Cates, M.C. Fishbein, H.S. Karagueuzian, P.S. Chen, and L.S. Chen (2004). **Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death.** *Journal of the American College of Cardiology* 43(5): 858-864. ISSN: 0735-1097.

NAL Call Number: RC681.A1

Abstract: OBJECTIVES: We sought to develop a high-yield canine model of sudden cardiac death (SCD). BACKGROUND: Because electrical stimulation is a powerful means to elicit nerve sprouting, we hypothesize that subthreshold electrical stimulation is more effective than nerve growth factor (NGF) infusion in inducing nerve sprouting and SCD in dogs with myocardial infarction (MI) and complete atrioventricular block (CAVB). METHODS: We gave subthreshold electrical stimulation to the left stellate ganglion (LSG) in six normal dogs for 41+-9 days (protocol 1) and to six dogs with MI and CAVB for 41+-29 days, while continuously monitoring their cardiac rhythm (protocol 2). We also monitored the rhythm of two dogs with MI, CAVB, and NGF infusion to the LSG and determined the ventricular nerve density in six healthy control dogs. RESULTS: In protocol 1, the hearts from dogs with LSG electrical stimulation had a higher density of nerve fibers immunopositive to tyrosine hydroxylase, synaptophysin, and growth-associated protein-43 than those of normal control dogs (p<0.01). In protocol 2, there was a high magnitude of cardiac nerve sprouting in all dogs studied. Ventricular tachycardia gtoreq8 beats and gtoreq20 beats was more frequent in dogs with electrical stimulation than in dogs with NGF infusion to the LSG (36+-60 and 11+-17 vs. 4.7+-6.1 and 0.1+-0.33 episodes per day, p<0.05 and p<0.03, respectively). Four of six dogs in protocol 2 had SCD. CONCLUSIONS: Subthreshold electrical stimulation of the LSG induces cardiac nerve sprouting and sympathetic hyperinnervation and facilitates the development of a high-yield canine model of ventricular arrhythmia and SCD.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, complete atrioventricular block, heart disease, therapy, myocardial infarction, heart disease, vascular disease, therapy, sudden cardiac death, long term subthreshold electrical stimulation, clinical techniques, therapeutic and prophylactic techniques.

Syuu, Y., H. Matsubara, T. Kiyooka, S. Hosogi, S. Mohri, J. Araki, T. Ohe, and H. Suga (2001). **Cardiovascular beneficial effects of electroacupuncture at Neiguan (PC-6) acupoint in anesthetized open-chest dog.** *Japanese Journal of Physiology* 51(2): 231-8. ISSN: 0021-521X.

NAL Call Number: QP34.5.J3

Abstract: Neiguan (PC-6) is a traditional acupoint in the bilateral forearms, overlying the median nerve trunk. Neiguan electroacupuncture (EA) has been believed to affect cardiovascular function and used in traditional Chinese medicine to improve or treat a wide range of health conditions and diseases, including angina pectoris, myocardial infarction, hypertension, and hypotension. However, few physiological studies have assessed the beneficial effects of Neiguan EA on the cardiovascular function. In the present study, we investigated its effects on the cardiovascular function in normal open-chest dogs under pentobarbital and fentanyl anesthesia. We also obtained left ventricular (LV) pressure-volume (P-V) data with a micromanometer catheter and a volumetric conductance catheter. Mean arterial pressure, end-diastolic volume, heart rate, stroke volume, cardiac output, and end-systolic pressure gradually decreased by 5 to 10% over 1.5 h without Neiguan EA. Neiguan EA at 40 Hz, however, increased these cardiovascular variables by 10 to 15%, especially end-systolic elastance (Ees) by 40% ($p<0.05$) over 15 to 60 min. After Neiguan EA was stopped at 1 h, these facilitated cardiovascular variables decreased below the pre-EA level. This beneficial effect of electroacupuncture may contribute to the effectiveness of the acupuncture in Chinese medicine.

Descriptors: animal model, Neiguan electroacupuncture, traditional acupoints, cardiovascular function, pentobarbital, fentanyl,anesthesia, left ventricular (LV) pressure-volume (P-V) data, micromanometer catheter, mean arterial pressure, end-diastolic volume, heart rate, stroke volume, cardiac output, end-systolic pressure.

Thomsen, M.B., P.G.A. Volders, M. Stengl, R.L. Spatjens, J.D.M. Beekman, U. Bischoff, M.A. Kall, K. Frederiksen, J. Matz, and M.A. Vos (2003). **Electrophysiological safety of sertindole in dogs with normal and remodeled hearts.** *Journal of Pharmacology and Experimental Therapeutics* 307(2): 776-784. ISSN: 0022-3565.

NAL Call Number: 396.8 J82

Abstract: Inhibition of the potassium current IKr and QT prolongation are associated with drug-induced torsades de pointes arrhythmias (TdP) and sudden cardiac death. We investigated the cardiac electrophysiological effects of sertindole, an antipsychotic drug reported to prolong the QT interval in schizophrenic patients. In cell cultures, sertindole seemed to be a selective blocker of IHERG over other ion currents. For IHERG, the IC50 value was 64 +- 7 nM, whereas ISCN5A, ICa,L, ICa,T, IKCNQ1/KCNE1, and IKv4.3 were blocked in the micromolar range. In canine ventricular myocytes, the IC50 value for IKr inhibition by sertindole was 107 +- 21 nM. Action potentials in these cells prolonged in a reverse rate- and concentration-dependent manner at 10 to 300 nM sertindole. In vivo, sertindole was administered to anesthetized dogs at clinically relevant (0.05-0.20 mg/kg) and high doses (1.0-2.0 mg/kg) i.v. At 0.05 to 0.20 mg/kg sertindole (plasma concentrations 30-157 nM), QTc was prolonged by 1 to 5% in normal dogs and by 9 to 20% in dogs with remodeled hearts due to chronic atrioventricular block (CAVB). TdP was not induced at these doses in normal dogs or in CAVB dogs with reproducible induction of TdP by dofetilide in previous experiments.

At 1.0 to 2.0 mg/kg sertindole (plasma concentrations 0.5-3.1 muM), QTc prolonged by 6 to 11% in normal dogs and by 22% in dofetilide-sensitive CAVB dogs. TdP occurred in three of five animals in the latter group. Thus, at high i.v. doses sertindole can pose a serious proarrhythmic risk when electrical remodeling of the ventricles is present. At clinically relevant doses, however, sertindole does not cause TdP in anesthetized dogs with normal or remodeled hearts.

Descriptors: behavior, cardiovascular system, transport and circulation, pharmacology, schizophrenia, behavioral and mental disorders, drug therapy, sudden cardiac death, heart disease, toxicity, drug induced, prevention and control, torsades de pointes arrhythmias, drug induced, prevention and control, electrophysiology, clinical techniques, i ca,l current, i ca,t current, i herg current, i kcnq1, kcne1 current, i kv4.3 current, i scn5a current, qt prolongation, chronic atrioventricular block.

Torp, R., E. Head, N.W. Milgram, F. Hahn, O.P. Ottersen, and C.W. Cotman (2000). **Ultrastructural evidence of fibrillar beta-amyloid associated with neuronal membranes in behaviorally characterized aged dog brains**. *Neuroscience* 96(3): 495-506. ISSN: 0306-4522.

Abstract: The aged dog brain accumulates beta-amyloid in the form of diffuse senile plaques, which provides a potentially useful in vivo model system for studying the events surrounding the deposition of beta-amyloid. We used postembedding immunocytochemistry at the electron microscopic level to determine the subcellular distribution of beta-amyloid 1-40 and beta-amyloid 1-42 peptides in the prefrontal and parietal cortex of behaviorally characterized dogs ranging in age from one to 17 years. Immunogold particles signaling beta-amyloid 1-42 occurred over intracellular and extracellular fibrils that were approximately 8 nm in width. Intracellular beta-amyloid 1-42 fibrils were found in close proximity to glial fibrillary acidic protein fibers within astrocytes, but only in cells with signs of plasma membrane disruption. Neuronal labeling of beta-amyloid 1-42 appears to be associated with the plasma membrane. Membrane-bound beta-amyloid 1-42 occurs in the form of fine fibrils that are embedded in the dendritic membrane and appear to project into the extracellular space as determined by quantitative analysis of the immunogold particle distribution. Bundles of beta-amyloid 1-42 were also closely associated and/or integrated with degenerating myelin sheaths of axons. In one dog that was impaired on several cognitive tasks, extensive beta-amyloid 1-42 deposition was associated with microvacuolar changes and vascular pathology. The present findings suggest that beta-amyloid 1-42 may be generated at the dendritic plasma membrane as well as in intracellular compartments. The close association between beta-amyloid 1-42 destroyed myelin suggests one possible new mechanism by which beta-amyloid 1-42 induces neurodegeneration.

Descriptors: nervous system, neural coordination, neurodegeneration, nervous system disease.

Traystman, R.J. (2003). **Animal models of focal and global cerebral ischemia.** *ILAR Journal* 44(2): 85-95. ISSN: 1084-2020.

NAL Call Number: QL55.A1I43

Abstract: The use of appropriate animal models is essential to predict the value and effect of therapeutic approaches in human subjects. Focal (stroke) and global (cardiac arrest) cerebral

ischemia represents diseases that are common in the human population. Stroke and cardiac arrest, which are major causes of death and disability, affect millions of individuals around the world and are responsible for the leading health care costs of all diseases. Understanding the mechanisms of injury and neuroprotection in these diseases is critical if we are ever to learn new target sites to treat ischemia. There are many animal models available to investigate injury mechanisms and neuroprotective strategies. This review summarizes many (but not all) small and large animal models of focal and global cerebral ischemia and discusses their advantages and disadvantages.
Descriptors: animal models, stroke, focal, global, cerebral ischemia, injury, neuroprotection.

Varenika, V., P. Dickinson, J. Bringas, R. LeCouteur, R. Higgins, J. Park, M. Fiandaca, M. Berger, J. Sampson, and K. Bankiewicz (2008). **Detection of infusate leakage in the brain using real-time imaging of convection-enhanced delivery.** *Journal of Neurosurgery* 109(5): 874-80. ISSN: 0022-3085.
Abstract: OBJECT: The authors have shown that convection-enhanced delivery (CED) of gadoteridol-loaded liposomes (GDLs) into different regions of normal monkey brain results in predictable, widespread distribution of this tracking agent as detected by real-time MR imaging. They also have found that this tracking technique allows monitoring of the distribution of similar nanosized agents such as therapeutic liposomes and viral vectors. A limitation of this procedure is the unexpected leakage of liposomes out of targeted parenchyma or malignancies into sulci and ventricles. The aim of the present study was to evaluate the efficacy of CED after the onset of these types of leakage. METHODS: The authors documented this phenomenon in a study of 5 nonhuman primates and 7 canines, comprising 54 CED infusion sessions. Approximately 20% of these infusions resulted in leakage into cerebral ventricles or sulci. All of the infusions and leakage events were monitored with real-time MR imaging. The authors created volume-distributed versus volume-infused graphs for each infusion session. These graphs revealed the rate of distribution of GDL over the course of each infusion and allowed the authors to evaluate the progress of CED before and after leakage. RESULTS: The distribution of therapeutics within the target structure ceased to increase or resulted in significant attenuation after the onset of leakage. CONCLUSIONS: An analysis of the cases in this study revealed that leakage undermines the efficacy of CED. These findings reiterate the importance of real-time MR imaging visualization during CED to ensure an accurate, robust distribution of therapeutic agents.
Descriptors: brain physiopathology, contrast media administration and dosage, convection, drug delivery systems methods, heterocyclic compounds administration and dosage, organometallic compounds administration and dosage, brain pathology, contrast media pharmacokinetics, dogs, heterocyclic compounds pharmacokinetics, liposomes pharmacokinetics, macaca fascicularis, magnetic resonance imaging, models, animal, organometallic compounds pharmacokinetics.

Wang, Q., Z. Wang, P. Zhu, and J. Jiang (2004). **Alterations of myelin basic protein and ultrastructure in the limbic system at the early stage of trauma-related stress disorder in dogs**. *Journal of Trauma Injury Infection and Critical Care* 56(3): 604-610. ISSN: 1079-6061.
Abstract: Background: The secondary injury and related complications after trauma are still the focus of trauma research. However, whether the remote effects on the central nervous

system could be induced by high-energy missile extremity impact remains unclear. Also, the possible biomarker for brain damage in traumatic stress disorder has not been determined. Methods: Forty-two healthy adult dogs were divided into three groups: the control group (n = 12), the high-speed trauma group (n = 15), and the low-speed trauma group (n = 15). Bilateral thighs of dogs were wounded with a smoothbore 6.2-mm rifle at a speed of 1,368 m/s (1.03-g steel bullet) for the high-speed trauma group and 625 m/s for the low-speed trauma group. The expression of myelin basic protein (MBP) in cerebrospinal fluid (CSF), hypothalamus and hippocampus of the limbic system, and temporoparietal cortex was investigated by enzyme-linked immunosorbent assay and dot-blot analysis. Also, the ultrastructure of the above areas was observed with light and electron microscopy. Results: Neuronal degeneration and nerve fiber demyelination were seen in the hypothalamus and hippocampus in the high-speed trauma group at 8 hours after impact. The MBP level was markedly increased in the CSF ($p < 0.01$) in the two trauma groups, in the hypothalamus of the low-speed trauma group ($p < 0.05$), and in both the hypothalamus and the hippocampus of the high-speed trauma group (p 0.01). The expression of MBP mRNA was also significantly enhanced in these areas at the same time. The increase of MBP content in the CSF was positively correlated with the elevation of MBP concentration in the hypothalamus and hippocampus. Conclusion: The hypothalamus and hippocampus of the limbic system in the central nervous system are vulnerable to damage after high-energy missile extremity impact, indicating that it might be one of the important pathologic bases involved in the development of trauma-related complications. Meanwhile, the MBP level in the CSF may be a sensitive biological indicator for brain damage at the early stage of trauma-related stress disorder.
Descriptors: nervous system, neural coordination, brain damage, injury, neoplastic disease, diagnosis, trauma related stress disorder, injury, diagnosis, pathology, symptom, dot blot analysis, laboratory techniques, enzyme linked immunosorbent assay, immunologic techniques, laboratory techniques.

Yamato, O., Y. Masuoka, M. Yonemura, A. Hatakeyama, H. Satoh, A. Kobayashi, M. Nakayama, T. Asano, T. Shoda, M. Yamasaki, K. Ochiai, T. Umemura, and Y. Maede (2003). **Clinical and clinico-pathologic characteristics of shiba dogs with a deficiency of lysosomal acid beta-galactosidase: a canine model of human gm1 gangliosidosis.** *Journal of Veterinary Medical Science* 65(2): 213-217. ISSN: 0916-7250.
NAL Call Number: SF604.J342
Abstract: The present study was conducted to determine the clinical and clinico-pathologic characteristics of Shiba dogs with GM1 gangliosidosis, which is due to an autosomal recessively inherited deficiency of lysosomal acid beta-galactosidase activity. Clinical and clinico-pathological features were investigated in 10 homozygous Shiba dogs with GM1 gangliosidosis. The age at onset was 5 to 6 months and the dogs manifested progressive neurologic signs including loss of balance, intermittent lameness, ataxia, dysmetria and intention tremor of the head. The dogs were unable to stand by 10 months of age due to a progression of ataxia and spasticity in all limbs. Corneal clouding, a visual defect, generalized muscle rigospasticity, emotional disorder and a tendency to be lethargic were observed at 9 to 12 months. The dogs became lethargic from 13 months of age. The survival period seemed to be 14 to 15 months. As a clinico-pathologic feature, lymphocytes with abnormally large vacuoles were observed in peripheral blood (30 to 50% of total lymphocytes) through the lifetime

of the dogs. The clinical and clinico-pathologic characteristics of this animal model are useful for not only the development and testing of potential methods of therapy, but also the diagnosis of affected homozygous Shiba dogs in veterinary clinics.
Descriptors: pathology, beta galactosidase, clinical aspects, disease models, dog breeds, enzyme activity, gangliosidosis, survival, metabolism, nervous system, neural coordination, veterinary medicine, medical sciences, GM1 gangliosidosis, genetic disease, metabolic disease, ataxia, nervous system disease, corneal clouding, eye disease, dysmetria, emotional disorder, behavioral and mental disorders, generalized muscle rigospasticity, tremor, balance loss, lameness, lethargy .

Yang, X.P. and S. Chiba (2003). **Interaction between neuropeptide y y1 receptors and alpha1b-adrenoceptors in the neurovascular junction of canine splenic arteries.** *European Journal of Pharmacology* 466(3): 311-315. ISSN: 0014-2999.
NAL Call Number: QP901.E8
Abstract: Previous study has demonstrated that periarterial electrical nerve stimulation (30-s trains of pulses at a frequency of 1 or 4 Hz) induces a double-peaked vasoconstriction consisting of an initial transient, predominantly P2X-receptor-mediated constriction followed by a prolonged, mainly alpha1-adrenoceptor-mediated response in the isolated canine splenic artery. Treatment with 8-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-8-azaspiro(4.5) decane-7,9-dione (BMY 7378, 0.1 mumol/l), a selective alpha1D-adrenoceptor antagonist, produced a slight but significant inhibition of the second peaked responses. A marked inhibition of second peaked responses was obtained by exposure of the tissues to chloroethylclonidine (60 mumol/l), an alpha1B- and alpha1D-adrenoeptor antagonist. Neither BMY 7378 nor chloroethylclonidine affected the first peaked vasoconstrictor responses. (Leu31,Pro34)Neuropeptide Y (10-30 nmol/l), a selective neuropeptide Y Y1 receptor agonist, enhanced the second peaked responses in the presence of BMY 7378 but failed to enhance the responses in the presence of chloroethylclonidine. The results indicate that the postjunctional alpha1B-adrenoceptor subtype is likely coupled to neuropeptide Y Y1 receptors responsible for the cooperation of the sympathetic adrenergic and neuropeptide Yergic transmission in the canine splenic artery.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology .

Yasukawa, T. (2002). **Effects of inversed ratio ventilation (irv) on intracranial pressure (icp) in dogs with pulmonary edema.** *Kawasaki Igakkai Shi* 28(4): 269-278. ISSN: 0386-5924.
Abstract: Although correlation between variations in the inspiratory to expiratory ratio (I:E ratio) and intracranial pressure (ICP) has not been clarified, the study of Mihira showed that IRV (at I:E ratios of 1.7:1, 2.3:1, and 4:1) does not influence ICP in dogs with normal or elevated ICP. In order to estimate the influence of lowered lung compliance on ICP during IRV, an additional study was designed to observe the effects of the I:E ratio=1:2 to 4:1 on ICP in 10 dogs with pulmonary edema induced by Oleic acid. Following baseline measurement of control ventilation (I:E ratio=1:2), lung edema was induced by venous injection of Oleic acid (0.05 mL/kg). After verifying the reduction of lung compliance, four different I:E ratios were applied in the order of I:E=1:2, 1.7:1, 2.3:1, and 4:1. Throughout the period of these measurements, PaCO2 constantly maintained normocapnia and arterial blood pressure

was kept within normal range. Intracranial hemodynamics (ICP, cerebral perfusion pressure), lung mechanics (mean airway pressure (mAWP), peak inspiratory pressure (PIP), lung compliance), systemic hemodynamics (mean arterial pressure, mean pulmonary artery pressure, central venous pressure, cardiac output), and blood gases were measured at 30 min under every I:E ratio ventilatory mode. In these dogs with pulmonary edema, mAWP significantly increased during IRV in comparison with that during control ventilation ($p<0.05$), but there was no significant difference in PIP between control ventilation and IRV. ICP remained unchanged during IRV (12.5+-4.2, 10.0+-2.9, 11.1+-2.2, 11.3+-2.7 at I:E=1:2, 1.7:1, 2.3:1 and 4:1, respectively). This study suggested that IRV (at I:E ratios of 1.7:1, 2.3:1, and 4:1), which can minimize ventilator-induced lung injury, has no influence on ICP. Therefore, IRV may be one beneficial option as ventilation strategy for acute respiratory distress syndrome with intracranial hypertension.
Descriptors: methods and techniques, nervous system, neural coordination, respiratory system, respiration, acute respiratory distress syndrome, respiratory system disease, intracranial hypertension, nervous system disease, vascular disease, pulmonary edema, inversed ratio ventilation, laboratory techniques, intracranial pressure, mean airway pressure.
Language of Text: Japanese.

Yelmen, N.K., G. Sahin, T. Oruc, and M. Hacibekiroglu (2003). **Hypoxic initiation of pulmonary hypertension is mediated by serotonin secretion from neuroepithelial bodies in chemodenervated dogs.** *Chinese Journal of Physiology* 46(1): 27-33. ISSN: 0304-4920.
Abstract: The purpose of this study was to investigate the stimulatory effect of hypoxia on the secretion of serotonin by neuroepithelial bodies (NEB) as well as to determine the relation between its level and changes in pulmonary arterial pressure (PAP) and also to determinate the effect of serotonin antagonists (pizotifen and methysergide) on the responses of pulmonary and systemic arterial pressures. The experiments were carried out in peripheral chemoreceptor-denervated dogs anesthetized with Na penthabarbital (30 mg/kg i.v.). On the breathing of normoxic and hypoxic (7% O2-93% N2) gas mixtures and on the injection of KCN (80 mug/kg i.v.), PAP, systemic arterial blood pressure (BP), tidal volume (VT), respiratory frequency (f/min), ventilation minute volume (VE) were determined. Also PAP and BP were recorded before and after the injection of pizotifen (0.5 mg/kg i.v.) and methysergide (1 mg/kg i.v.) during normoxic or hypoxic gas mixture breathing. At the end of each experimantal phase, serotonin level, PaO2, PaCO2 and pHa values in blood samples obtained from left ventricle and femoral artery were determined. On the breathing of the hypoxic gas mixture of the chemodenervated dogs, VT, VE and BP significantly decreased ($P<0.001$, $P<0.001$, $P<0.01$). The mean value of PAP and serotonin levels (ventricular and femoral) were found significantly increased when compared with the corresponding normoxic values ($P<0.001$, $P<0.05$). On the other hand, injection of KCN produced no significant changes in PAP, serotonin levels, BP and respiratory parameters. After the injection of pizotifen, PAP was significantly increased in hypoxia ($P<0.01$). After the injection of methysergide, the response of PAP was completely abolished during the breathing of hypoxic gas mixture. The finding of the abolition of response of PAP to hypoxia after the injection of methysergide indicates that serotonin release from NEB may be responsible for the elevation of PAP in hypoxic hypoxia.
Descriptors: cardiovascular system, transport and circulation, nervous system, neural coor-

dination, respiratory system, respiration, veterinary medicine, medical sciences, hypoxia, respiratory system disease, pulmonary hypertension, chemodenervation, experimental surgical techniques, laboratory techniques, pulmonary arterial pressure [pap].

Zhong, H., B. Chen, S. Lu, M. Zhao, Y. Guo, and S. Hou (2007). **Nerve regeneration and functional recovery after a sciatic nerve gap is repaired by an acellular nerve allograft made through chemical extraction in canines.** *Journal of Reconstructive Microsurgery* 23(8): 479-87. ISSN: 0743-684X.

Abstract: The purpose of the present study is to test whether chemically extracted acellular nerve segments can be used to repair the sciatic nerve gap. Fifteen canines were divided into acellular nerve allografting group (ANG, six canines), autografting group (AG, six canines), and fresh nerve allografting group (FNG, three canines). The sciatic nerves on the right side of the animals were exposed, and 5-cm-long segments of the nerves were removed from the midthigh level and replaced by the three types of grafts. At 6 months after grafting, all animals in the ANG and AG had similar patterns of right posterior limb gait cycle and right ankle movements. Moreover, the animals in the ANG and AG had similar nerve regeneration, with dense regeneration fibers in the distal tibial nerves and obvious motor end plates in the target muscle. But in FNG, the area surrounding the graft was scarred as the result of inflammation, and there was a brown central area where there was little nerve regeneration. All of the above shows that chemical acellular nerve allografting can be used to repair a gap as long as 5 cm in the continuity of the sciatic nerve in canines and has similar effects to autografting.

Descriptors: nerve regeneration physiology, sciatic nerve physiology, axons ultrastructure, basement membrane transplantation, deoxycholic acid, detergents, dogs, electrophysiology, evoked potentials, motor, evoked potentials, somatosensory, gait, models, animal, nerve fibers, neural conduction, octoxynol, recovery of function, sciatic nerve injuries, sciatic nerve surgery, transplantation, autologous, transplantation, homologous.

Zhou, C., M. Yamaguchi, G. Kusaka, C. Schonholz, A. Nanda, and J.H. Zhang (2004). **Caspase inhibitors prevent endothelial apoptosis and cerebral vasospasm in dog model of experimental subarachnoid hemorrhage**. *Journal of Cerebral Blood Flow and Metabolism* 24(4): 419-431. ISSN: 0271-678X.

Abstract: Apoptosis in the endothelium of major cerebral arteries may play a role in the initiation and maintenance of cerebral vasospasm after subarachnoid hemorrhage (SAH). We tested the therapeutic effect of caspase inhibitors on endothelial apoptosis and on cerebral vasospasm in an established dog double-hemorrhage model. Thirty-one mongrel dogs were divided into five groups: control; SAH; SAH treated with vehicle (DMSO); SAH treated with Ac-DEVD-CHO (a specific caspase-3 inhibitor) and SAH treated with Z-VAD-FMK (a broad caspase inhibitor). The inhibitors (100 muM) were injected into the cisterna magna daily front Day 0 through Day 3. Angiography was performed on Day 0 and Day 7. Histology, TUNEL staining, and immunohistochemistry were conducted on basilar arteries collected on Day 7 after SAH. Positive staining of TUNEL, poly(ADP)-ribose polymerase (PARP), caspase-3, and caspase-8 was observed in the endothelial cells of the spastic arteries. Double fluorescence labeling demonstrated colocalization of TUNEL with caspase-3 and TNFalpha-receptor-1 (TNFR I). Ac-DEVD-CHO and Z-VAD-FMK prevented endothelial

apoptosis and reduced angiographic vasospasm. The mechanism of apoptosis in endothelial cells involves TNFR1 and the caspase-8 and caspase-3 pathways. Caspase inhibitors may have potential in the treatment of cerebral vasospasm..
Descriptors: biochemistry and molecular biophysics, subarachnoid hemorrhage, nervous system disease, vascular disease, tunel, genetic techniques, laboratory techniques, cerebral vasospasm, endothelial apoptosis.

Zuperku, E.J., I.F. Brandes, A.G. Stucke, A. Sanchez, F.A. Hopp, and E.A. Stuth (2008). **Major components of endogenous neurotransmission underlying the discharge activity of hypoglossal motoneurons in vivo.** *Advances in Experimental Medicine and Biology* 605: 279-84. ISSN: 0065-2598.
NAL Call Number: QP901 .A33
Abstract: Multibarrel micropipettes were used to simultaneously record unit activity and apply antagonists on individual inspiratory hypoglossal motoneurons (IHMNs) to determine the endogenous activation levels of NMDA, non-NMDA, GABA(A) and serotonin receptors responsible for the IHMN spontaneous discharge patterns in decerebrate dogs. IHMN activity is highly dependent on glutamatergic phasic and tonic drives, which are differentially mediated by the receptor subtypes. Endogenous serotonin significantly amplifies IHMN activity, while GABAergic gain modulation acts to attenuate activity. Thus, alterations in the neurotransmission of any of these systems could markedly alter neuronal output to target muscles.
Descriptors: hypoglossal nerve physiology, motor neurons physiology, synaptic transmission physiology, 2 amino 5 phosphonovalerate pharmacology, bicuculline pharmacology, decerebrate state, dogs, excitatory amino acid antagonists pharmacology, ketanserin pharmacology, models, animal, models, neurological, quinoxalines pharmacology, tongue innervation.

Oncology

Akhtar, N., M.L. Padilla, E.B. Dickerson, H. Steinberg, M. Breen, R. Auerbach, and S.C. Helfand (2004). **Interleukin-12 inhibits tumor growth in a novel angiogenesis canine hemangiosarcoma xenograft model**. *Neoplasia* 6(2): 106-116. ISSN: 1522-8002.

Abstract: We established a canine hemangiosarcoma cell line derived from malignant endothelial cells comprising a spontaneous tumor in a dog to provide a renewable source of endothelial cells for studies of angiogenesis in malignancy. Pieces of the hemangiosarcoma biopsy were engrafted subcutaneously in a bg/nu/XID mouse allowing the tumor cells to expand in vivo. A cell line, SB-HSA, was derived from the xenograft. SB-HSA cells expressed vascular endothelial growth factor (VEGF) receptors 1 and 2, CD31, CD146, and alphavbeta3 integrin, and produced several growth factors and cytokines, including VEGF, basic fibroblast growth factor, and interleukin (IL)-8 that are stimulatory to endothelial cell growth. These results indicated that the cells recapitulated features of mitotically activated endothelia. In vivo, SB-HSA cells stimulated robust angiogenic responses in mice and formed tumor masses composed of aberrant vascular channels in immunocompromised mice providing novel opportunities for investigating the effectiveness of antiangiogenic agents. Using this model, we determined that IL-12, a cytokine with both immunostimulatory and antiangiogenic effects, suppressed angiogenesis induced by, and tumor growth of, SB-HSA cells. The endothelial cell model we have described offers unique opportunities to pursue further investigations with IL-12, as well as other antiangiogenic approaches in cancer therapy.

Descriptors: pharmacology, tumor biology, spontaneous tumor, hemangiosarcoma cell line, cancer therapy, basic fibroblast growth factor, antiangiogenic effects.

Aniola, J., S.H. Selman, L. Lilge, R. Keck, and J. Jankun (2003). **Spatial distribution of liposome encapsulated tin etiopurpurin dichloride (snet2) in the canine prostate: implications for computer simulation of photodynamic therapy.** *International Journal of Molecular Medicine* 11(3): 287-291. ISSN: 1107-3756.

Abstract: Photodynamic therapy (PDT) is a minimally invasive treatment that can be employed in many human diseases including prostate cancer. PDT for prostate cancer depends on the sequestration of a photosensitizing drug within the glandular tissue. The photosensitizer is subsequently activated by light (usually from a laser) and the active drug destroys tissue. Since prostate cancer is a multifocal disease, PDT must ablate the glandular prostate completely. This will depend on the precise placement of light sources in the prostate and delivery of a therapeutic light dose to the entire gland. Also, sources of light and their spatial distribution must be tailored to each individual patient. The uniform, therapeutic light distribution can be achieved by interstitial light irradiation. In this case, the light is delivered by diffusers placed within the substance of the prostate parallel to the urethra at a distance optimized to deliver adequate levels of light and to create the desired photodynamic effect. To help achieve the uniform light distribution throughout the prostate we have developed a computer program that can determine treatment effects. The program predicts

the best set of parameters and the position of light diffusers in space, and displays them in graphical or in numerical form assuming a fixed attenuation coefficient. The two parameters of greatest importance in the computer simulation are attenuation coefficient and critical fluence. Both depend on the concentration of active drug within the prostate gland. It is necessary to know the nature of the spatial distribution of photosensitizer within the prostate to execute computer modeling of PDT with high precision. We found that the concentration of SnET2 is heterogeneous in nature, and is higher in the proximity of the glandular capsule. It is clear therefore that any future attempts of computerized modeling of this procedure must take into consideration the uneven sequestration of photosensitizer and the consequential asymmetrical necrosis of the prostate.
Descriptors: models and simulations, computational biology, radiation biology, reproductive system, reproduction, tumor biology, prostate cancer, neoplastic disease, reproductive system disease, male, urologic disease, radiotherapy, photodynamic therapy, clinical techniques, therapeutic and prophylactic techniques, computer simulation.

Boonsoda, S. and P. Wanikiat (2008). **Possible role of cyclooxygenase-2 inhibitors as anticancer agents.** *Veterinary Record* 162(5): 159-61. ISSN: 0042-4900.
NAL Call Number: 41.8 V641
Descriptors: cyclooxygenase 2 metabolism, cyclooxygenase 2 inhibitors therapeutic use, neoplasms drug therapy, neoplasms metabolism, cyclooxygenase 2 genetics, dogs, gene expression regulation, neoplastic, models, animal.

Breen, M. (2008). **Canine cytogenetics: from band to basepair.** *Cytogenetic and Genome Research* 120(1-2): 50-60. ISSN: 1424-8581.
NAL Call Number: QH431 .C95
Abstract: Humans and dogs have coexisted for thousands of years, during which time we have developed a unique bond, centered on companionship. Along the way, we have developed purebred dog breeds in a manner that has resulted unfortunately in many of them being affected by serious genetic disorders, including cancers. With serendipity and irony the unique genetic architecture of the 21st century genome of Man's best friend may ultimately provide many of the keys to unlock some of nature's most intriguing biological puzzles. Canine cytogenetics has advanced significantly over the past 10 years, spurred on largely by the surge of interest in the dog as a biomedical model for genetic disease and the availability of advanced genomics resources. As such the role of canine cytogenetics has moved rapidly from one that served initially to define the gross genomic organization of the canine genome and provide a reliable means to determine the chromosomal location of individual genes, to one that enabled the assembled sequence of the canine genome to be anchored to the karyotype. Canine cytogenetics now presents the biomedical research community with a means to assist in our search for a greater understanding of how genome architectures altered during speciation and in our search for genes associated with cancers that affect both dogs and humans. The cytogenetics 'toolbox' for the dog is now loaded. This review aims to provide a summary of some of the recent advancements in canine cytogenetics. Copyright 2008 S. Karger AG, Basel.

Descriptors: genetic disorders, cancer, animal models, canine genome, chromosomal location, gene sequence

Cooley, D.M., D.L. Schlittler, L.T. Glickman, M. Hayek, and D.J. Waters (2003). **Exceptional longevity in pet dogs is accompanied by cancer resistance and delayed onset of major diseases.** *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 58(12): B1078-84. ISSN: 1079-5006.

Abstract: To characterize extreme aged pet dogs as a first step in developing an animal model of exceptional longevity, we constructed lifetime medical histories for 345 Rottweiler dogs using information collected from owners and veterinarians. Extreme aged dogs (alive at the 95th percentile age at death for the study population, > or =13.3 years) were compared with a usual longevity group (9-10 years). Exceptional longevity in Rottweiler dogs was accompanied by a significant delay in the onset of major life-threatening diseases; 76% of extreme aged dogs remained free of all major diseases during the first 9 years of life. Only 19% of extreme aged dogs died of cancer versus 82% of dogs with usual longevity (p <.0001). The reduction in cancer mortality in oldest-old pet dogs mimics that seen in human centenarians and provides strong rationale for using this animal model to study comparative mechanisms of cancer resistance in the extreme aged.

Descriptors: animal model, longevity, aging, medical history, cancer resistance.

De Vico, G. and P. Mairolino (2008). **Canine and Feline Models for Cancer**. M. Conn *Sourcebook of Models for Biomedical Research,* Humana Press: Totowa, N.J.: London: Springer, p. 677-682.

NAL Call Number: R853.A53 S68 2008

Descriptors: cat, dogs, animal models, canine non-Hodgkins lymphoma, oral malignant melanoma, osteosarcomas, tumor development.

Eisenschenk, A., C. Witzel, M. Lautenbach, A. Ekkernkamp, U. Weber, and M.V. Kuntscher (2007). **Does chemotherapy impair the bone healing and biomechanical stability of vascularized rib and fibula grafts?** *Journal of Reconstructive Microsurgery* 23(1): 35-40. ISSN: 0743-684X.

Abstract: The purpose of this study was to observe the impact of chemotherapy on the healing and biomechanical properties of vascularized bone grafts. Ten male beagle dogs were divided into two experimental groups: a chemotherapy group (CH) and control group (C). Group CH received adjuvant and neo-adjuvant chemotherapy. Each animal of both groups underwent the following operative procedures. The 5th and 7th rib were removed and replaced by vascularized pedicle transfers of the adjacent 4th and 8th rib. Additionally, a free fibular flap was elevated and retransferred to the same anatomic position. The rate of bony union on plain x-ray was 100 percent in group C, 30 percent in the vascularized rib, and 80 percent in the fibula grafts of group CH. Microangiography demonstrated no avascular bone segments in group C and in the fibula flaps of group CH. The vascularized ribs of group CH presented with 20 percent avascular bone segments. Biomechanical tests focusing on the durability of the vascularized grafts against bending and torsion forces demonstrated a reduction of the average maximum bending times by 17 percent and 23.9 percent compared to the controls (P < 0.05). The twisting times were reduced by 13.8 percent (n.s.) and 32.5 percent

($P < 0.05$). The data demonstrated a clear worsening in bone healing and stability after simulated adjuvant and neo-adjuvant chemotherapy. Thus, a large animal model was established for the further determination of the effects of chemotherapy on different vascularized bone transfers.

Descriptors: antineoplastic agents pharmacology, bone transplantation pathology, bone and bones drug effects, angiography, antibiotics, antineoplastic pharmacology, antimetabolites, antineoplastic pharmacology, biomechanics, chemotherapy, adjuvant, dogs, doxorubicin pharmacology, fibula, methotrexate pharmacology, microradiography, models, animal, neo-adjuvant therapy, pliability, ribs, torque, wound healing drug effects.

Ensminger, W., J. Knol, S. Deremer, E. Wilkinson, S. Walker, D. Williams, and J. Maybaum (2004). **Effects of dexamethasone or celecoxib on biliary toxicity after hepatic arterial infusion of 5-fluorodeoxyuridine in a canine model.** *Cancer Research* 64(1): 311-315. ISSN: 0008-5472.

NAL Call Number: 448.8 C16

Abstract: Previous work has shown that in humans the dose-limiting toxicity for fluorodeoxyuridine (2-fluoro-5'-deoxyuridine (FdUrd)) when administered by hepatic arterial infusion is biliary sclerosis. The current study was undertaken to attempt to modify this toxicity in a canine model that has been demonstrated to closely mimic the clinical situation. Unlike previous studies using this model, in which animals were sacrificed after extensive fibrosis had already occurred, the current experiments were designed so that observations of pathology were made at an earlier time, when the initial inflammatory injury underlying the fibrotic process was still taking place. Implantable pumps were used to deliver FdUrd into the hepatic artery of animals at a rate of 0.3 mg/kg/day in the presence or absence of 10 mg/week dexamethasone or 100 mg/day of celecoxib for 35 days, at which time the animals were beginning to show signs of toxicity. After evaluation for radiological evidence of biliary obstruction, the animals were sacrificed and portions of their livers were processed for examination of microscopic pathology and 2-bromo-5'deoxyuridine labeling index. Dexamethasone treatment protected the animals from biliary sclerosis determined radiologically, further validating this model as being representative of the response in humans. Similarly the Cox-2 inhibitor, celecoxib, appeared to provide protection against radiological changes of biliary stricture, although possibly to a lesser degree than the resultant from dexamethasone. In addition, FdUrd treatment caused elevation of the DNA 2-bromo-5'deoxyuridine labeling index above control levels in biliary epithelial cells. Dexamethasone and celecoxib each significantly attenuated the FdUrd-induced elevation of DNA labeling index in biliary epithelium. These findings demonstrate the usefulness of this canine model for studying the mechanisms of drug-induced biliary sclerosis and reinforce the hypothesis that blocking inflammation may retard the progression of injury that eventually leads to fibrosis. This study suggests that clinical testing of celecoxib as a preventive for hepatic arterial-FdUrd induced biliary damage could prove valuable.

Descriptors: digestive system, ingestion and assimilation, pharmacology, veterinary medicine, medical sciences, biliary obstruction, digestive system disease, biliary sclerosis, drug induced, colorectal cancer, neoplastic disease, infusaid model 400 implantable pump, drug delivery device.

Erdelyi, I., D.H.M. Nieskens, J.E. Van Dijk, L. Vass, and H. Nederbragt (2003). **Immunohistochemical evaluation of versican, in relation to chondroitin sulphate, in canine mammary tumours.** *Histology and Histopathology* 18(4): 1067-1080. ISSN: 0213-3911.

Abstract: The expression of increased amounts of versican, a chondroitin sulphate proteoglycan, in neoplastic tissues may play a role in promoting tumour cell proliferation and migration. This study investigated the immunolocalization of versican in normal and neoplastic canine mammary tissues, using antibodies 12C5 and 2B1, against different epitopes of the protein core of versican. Antibody CS56, recognising chondroitin sulphate (CS), was used to investigate the relation between versican and CS, which accumulates in canine mammary tumours. We found enhanced versican expression in both benign and malignant tumours, appearing in three main patterns: in periductal tissues, probably in association with basement membranes of ducts; in peripheral invasive areas of malignant tumours; and in spindle cell proliferations and myxoid areas of complex and mixed tumours. The 12C5 and 2B1 immunoreactivities co-localised in all types of tumours, and could be improved by chondroitinase digestion. The only exception was the abundant extracellular matrix (ECM) of spindle cell proliferations, particularly in myxoid areas of complex and mixed tumours, which displayed intense and diffuse 12C5 immunoreactivity and patchy or absent 2B1 and CS56 immunoreactivities; versican immunoreactivity could not be enhanced by chondroitinase digestion. The results indicate that versican is one of the extracellular matrix components characteristic of canine mammary tumours. It appears likely that in complex and mixed tumours versican exists in at least two forms, one of them lacking the CS attachment domain and the 2B1 epitope. Furthermore, the enhanced versican expression in the invasive areas of malignant tumours indicates the involvement of this proteoglycan in tumour cell invasion.

Descriptors: tumor biology, mammary tumor, neoplastic disease, reproductive system disease, female, immunohistochemistry, immunologic techniques, laboratory techniques.

Hemminki, A., A. Kanerva, E.J. Kremer, G.J. Bauerschmitz, B.F. Smith, B. Liu, M. Wang, R.A. Desmond, A. Keriel, B. Barnett, H.J. Baker, G.P. Siegal, and D.T. Curiel (2003). **A canine conditionally replicating adenovirus for evaluating oncolytic virotherapy in a syngeneic animal model.** *Molecular Therapy* 7(2): 163-73. ISSN: 1525-0016.

NAL Call Number: RB155.8

Abstract: Oncolytic adenoviruses, which selectively replicate in and subsequently kill cancer cells, have emerged as a promising approach for treatment of tumors resistant to other modalities. Although preclinical results have been exciting, single-agent clinical efficacy has been less impressive heretofore. The immunogenicity of adenoviruses, and consequent premature abrogation of replication, may have been a partial reason. Improving the oncolytic potency of agents has been hampered by the inability to study host-vector interactions in immune-competent systems, since human serotype adenoviruses do not productively replicate in animal tissues. Therefore, approaches such as immunomodulation, which could result in sustained replication and subsequently increased oncolysis, have not been studied. Utilizing the osteocalcin promoter for restricting the replication of a canine adenovirus to dog osteosarcoma cells, we generated and tested the first nonhuman oncolytic adenovirus. This virus effectively killed canine osteosarcoma cells in vitro and yielded a therapeutic benefit

in vivo. Canine osteosarcoma is the most frequent malignant disease in large dogs, with over 8000 cases in the United States annually, and there is no curative treatment. Therefore, immunomodulation for increased oncolytic potency could be studied with clinical trials in this population. This could eventually translate into human trials.
Descriptors: animal model, immunomodulation, canine osterosarcoma,oncolytic adenoviruses, in vitro, therapy, in vivo.

Higginbotham, M., C. Henry, K. Katti, S. Casteel, P. Dowling, and N. Pillarsetty (2003). **Preclinical tolerance and pharmacokinetic assessment of MU-Gold, a novel chemotherapeutic agent, in laboratory dogs.** *Veterinary Therapeutics: Research in Applied Veterinary Medicine* 4(1): 76-82. ISSN: 1528-3593.
NAL Call Number: SF601 .V4745
Descriptors: dogs, gold, chemotherapy, pharmacokinetics, toxicity

Jahan Parwar, B., D.K. Chhetri, S. Hart, S. Bhuta, and G.S. Berke (2003). **Development of a canine model for recurrent respiratory papillomatosis.** *Annals of Otology Rhinology and Laryngology* 112(12): 1011-1013. ISSN: 0003-4894.
Abstract: A canine model for recurrent respiratory papillomatosis (RRP) was developed with canine oral papillomavirus (COPV) inoculated into the buccal mucosa and supraglottic larynx of 5 beagles. The animals received systemic immunosuppression with daily oral prednisone at doses of 0, 1, 2, 3, and 4 mg/kg. Buccal papillomata developed at 6 weeks in all animals and regressed by 10 weeks in the animals that received 0 and 1 mg/kg. The other animals had continuous growth of their buccal papillomata for 26 weeks. The animal that received 2 mg/kg developed papillomata on the lingual surface of the epiglottis that continued to grow through 26 weeks. Systemic oral prednisone successfully maintained COPV-induced oral and laryngeal papillomata in beagles. Thus, COPV-induced oral and laryngeal papillomata that are prednisone-maintained may have utility as a model for RRP.
Descriptors: oncology, human medicine, medical sciences, otolaryngology, human medicine, medical sciences, pulmonary medicine, human medicine, medical sciences, recurrent respiratory papillomatosis, neoplastic disease, respiratory system disease.

Kaewsakhorn, T., M. Gower, W. Kisseberth, C. Capen, M. Calverley, and N. Inpanbutr (2004). **Effects of calcitriol and medium chain triglyceride (mct) on cell growth of the canine transitional cell carcinoma of the urinary bladder (tcc) in vitro**. *FASEB Journal* 18(4-5): Abst. 68.8. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: calcitriol , cell biology, cell proliferation, pharmacology, tumor biology, bladder transitional cell carcinoma, neoplastic disease, urologic disease, therapy, western blot, genetic techniques, laboratory techniques, drug regimen.

Kangasniemi, M., R.J. Stafford, R.E. Price, E.F. Jackson, and J.D. Hazle (2003). **Dynamic gadolinium uptake in thermally treated canine brain tissue and experimental cerebral tumors.** *Investigative Radiology* 38(2): 102-107. ISSN: 0020-9996.
Abstract: RATIONALE AND OBJECTIVES: Thermal coagulation of cerebral tumors induces reactive changes within adjacent brain tissue, which appear as Gd-DTPA enhance-

ment in MR images. This makes assessment of therapeutic success difficult to establish radiographically because the reactive changes can mimic residual tumor. Dynamic Gd-DTPA uptake curves in reactive tissue and tumor were investigated to assess the utility of contrast enhanced (CE)-dynamic MRI to distinguish reactive changes from residual tumor in a canine model. MATERIALS AND METHODS: Cerebral thermal necrosis was induced using a 980 nm laser in 11 dogs with intracerebral transmissible venereal tumors (TVTs). A fast spin-echo T1-weighted imaging sequence was used for CE-dynamic MRI. Gd-DTPA uptake data were acquired with 10-second temporal resolution and for untreated TVTs for reactive tissue using a sigmoidal-exponential model. RESULTS: Characteristic gadolinium uptake curves were measured and characterized for reactive brain tissue, and untreated and treated TVTs. Both early and delayed dynamic responses were significantly different in reactive brain tissue compared with TVT. CONCLUSION: Reactive thermal changes in otherwise normal brain tissue can be distinguished from residual tumor after cerebral thermal therapy using CE -dynamic MRI.

Descriptors: nervous system, neural coordination, pharmacology, tumor biology, cerebral thermal necrosis, nervous system disease, intracerebral transmissible venereal tumor, neoplastic disease, radiotherapy, contrast enhanced dynamic magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, fast spin echo t1 weighted imaging, sigmoidal exponential model, mathematical and computer techniques, thermal coagulation therapy, therapeutic and prophylactic techniques, reactive thermal change.

Kent, M.S., B.R. Madewell, G. Dank, R. Dick, S.D. Merajver, and G.J. Brewer (2004). **An anticopper antiangiogenic approach for advanced cancer in spontaneously occurring tumors using tetrathiomolybdate: a pilot study in a canine animal model.** *Journal of Trace Elements in Experimental Medicine* 17(1): 9-20. ISSN: 0896-548X.

NAL Call Number: QP534.J68

Abstract: In this pilot study, 13 dogs of various breeds and ages with a variety of advanced tumors were treated with the antiangiogenic copper complexing drug tetrathiomolybdate. Dose escalations were performed to determine the safe and effective dose in dogs. The study was designed to last for a 6-month period for each dog entered. Dogs were examined weekly for the first 3 months and then every other week for the next 3 months. Complete blood count, serum biochemistry panel, and measurement of serum ceruloplasmin (Cp) content were conducted at each visit to monitor response to drug administration. Serum Cp was used as a surrogate marker of copper status. The owner reported toxicity at each visit. The dog was examined for physical abnormalities. Tumor measurements were completed every 2 weeks using direct measurements of the tumor with calipers in three planes or by direct measurements of the tumor using radiographic or ultrasonographic images in two planes. Tumor response was evaluated only after dogs achieved a 4-week reduction in their serum Cp content. Tumor responses were defined as either disease stabilization or reduction in tumor volume. Nine dogs achieved Cp reduction. Of those dogs, five had no response to treatment, whereas four dogs had tumor responses after Cp reduction, characterized as either disease stabilization or reduction in tumor volume, for the remainder of the study period. There was only mild self-limiting toxicity with use of the drug.

Descriptors: pharmacology, veterinary medicine, medical sciences, advanced cancer, neoplasms, neoplastic disease, drug therapy, spontaneously occurring tumor.

Lee, J.L., C.J. Chang, S.Y. Wu, D.R. Sargan, and C.T. Lin (2004). **Secreted frizzled-related protein 2 (SFRP2) is highly expressed in canine mammary gland tumors but not in normal mammary glands.** *Breast Cancer Research and Treatment* 84(2): 139-49. ISSN: 0167-6806.
Abstract: Canine mammary gland tumor (MGT) is the commonest tumor in female dogs and a good animal model of human breast cancer. A group of newly identified genes encoding secreted frizzled-related proteins (SFRP) have been implicated in apoptosis regulation and tumorigenesis. Canine mammary tissues from 50 spontaneous MGTs and 10 normal mammary glands (MGs) were obtained from surgically excised specimens and analyzed for expression of SFRP2, beta-catenin, and cyclin D1. By RT-PCR and in situ hybridization, SFRP2 gene was found abundantly expressed in neoplastic mammary tissues but not in normal mammary tissues, suggesting that SFRP2 may contribute as a tumor marker in canine MGTs. By immunohistochemical staining, the immunoreactivity of the SFRP2 protein was detected in more diverse areas than SFRP2 mRNA expression, including nuclei or/and cytoplasm and extracellular matrix of the tumor. In tumor masses, beta-catenin lost its tight association with the membrane and diffused into the nucleus. The expression of beta-catenin (79.4% positive) and cyclin D1 (71.4% positive) was also increased in MGTs. In the course of tumor progression, SFRP2 mRNA ($p < 0.05$) and beta-catenin protein ($p < 0.01$) steadily increased but not in cyclin D1. The level of SFRP2 was linearly correlated with its downstream target beta-catenin ($p < 0.05$), but not correlated with cyclin D1 ($p < 0.5$). As revealed in this study, the exclusive overexpression of SFRP2 in canine MGTs suggests that SFRP2 is a potential candidate gene for further investigation of mammary tumorigenesis and complex etiology of the canine model of mammary neoplasms.
Descriptors: animal model, female, breast cancer, secreted frizzled-related proteins (SFRP), apotosis regulation, tumorigenesis.

Lee, J.L., C.J. Chang, L.L. Chueh, and C.T. Lin (2003). **Expression of secreted frizzled-related protein 2 in a primary canine mammary tumor cell line: a candidate tumor marker for mammary tumor cells.** *In Vitro Cellular and Developmental Biology Animal* 39(5-6): 221-227. ISSN: 1071-2690.
NAL Call Number: QH585.A1I58
Abstract: Canine mammary tumors (CMTs) have been proposed to be a good animal model for human breast cancer. To provide a basis for the tumorigenic study of CMTs, cell lines were established using a modified cell culture technique. The epithelial morphology and immunostaining with cytokeratin 18 confirmed the epithelial origin of the cells. In an investigation of possible mammary tumorigenesis-related factors, the expression of Wnt signaling-related proteins was detected in cell lines. Secreted frizzled-related protein 2 (SFRP2) was abundantly expressed in CMT cells but not in normal canine mammary gland (MG) cells. Secreted frizzled-related protein 2 was secreted into the culture medium and was associated with the extracellular matrix. In addition, increased expressions of beta-catenin and cyclin D1 were observed in cells overexpressing SFRP2. The marked differential expression of SFRP2 reveals that this protein may be a potential candidate marker for CMTs. The CMT cell line established in this study provides a useful tool and experimental model for under-

standing both the tumorigenesis of CMTs and the role of Wnt signaling in cancers.
Descriptors: biochemistry and molecular biophysics, cell biology, reproductive system, reproduction, tumor biology, mammary tumor, neoplastic disease, pathology, immunostaining, immunologic techniques, laboratory techniques, primary culture, culturing techniques, wnt signaling, epithelial morphology, mammary tumorigenesis, animal model, breast cancer, canine mammary tumors, Secreted frizzled-related protein 2 (SFRP2).

Lilge, L., N. Pomerleau Dalcourt, A. Douplik, S.H. Selman, R.W. Keck, M. Szkudlarek, M. Pestka, and J. Jankun (2004). **Transperineal in vivo fluence-rate dosimetry in the canine prostate during snet2-mediated pdt**. *Physics in Medicine and Biology* 49(14): 3209-3225. ISSN: 0031-9155.
Abstract: Advances in photodynamic therapy (PDT) treatment for prostate cancer can be achieved either by improving selectivity of the photosensitizer towards prostate gland tissue or improving the dosimetry by means of individualized treatment planning using currently available photosensitizers. The latter approach requires the ability to measure, among other parameters, the fluence rate at different positions within the prostate and the ability to derive the tissue optical properties. Here fibre optic probes are presented capable of measuring the fluence rate throughout large tissue volumes and a method to derive the tissue optical properties for different volumes of the prostate. The responsivity of the sensors is sufficient to detect a fluence rate of 0.1 mW cm-2. The effective attenuation coefficient in the canine prostate at 660 nm is higher at the capsule (2.15 +/- 0.19 cm-1) than in proximity of the urethra (1.84 +/- 0.36 cm-1). Significant spatial and temporal intra- and inter-canine variability in the tissue optical properties was noted, highlighting the need for individualized monitoring of the fluence rate for improved dosimetry.
Descriptors: computational biology, reproductive system, reproduction, tumor biology, prostate cancer, neoplastic disease, reproductive system disease, male, urologic disease, photodynamic therapy, clinical techniques, therapeutic and prophylactic techniques, transperineal in vivo fluence rate dosimetry, laboratory techniques, attenuation coefficient, fluence rate, inter canine variability, intra canine variability, tissue optical properties.

Marsella, R. and C.F. Nicklin (2000). **Double-blinded cross-over study on the efficacy of pentoxifylline for canine atopy**. *Veterinary Dermatology* 11(4): 255-260. ISSN: 0959-4493.
NAL Call Number: SF901.V47
Abstract: The pathogenesis of canine atopy has not been established completely. Recent studies have shown that tumour necrosis factor alpha and Interleukin-6 play a role in allergic reactions in humans and mice. Pentoxifylline (PTX) suppresses synthesis of these cytokines and may be a useful therapy for modulating the symptoms of canine atopy. The objectives of this study were to investigate the effects of PTX (10 mg kg-1 twice daily for 4 weeks) on clinical signs (erythema and pruritus) and intradermal skin test reactivity in 10 atopic dogs. The study was a double-blinded, placebo controlled, crossover clinical trial with a washout period of 2 weeks between treatments. Clinical signs were evaluated and scored by the investigator and owners. During PTX treatment, scores of pruritus and erythema decreased significantly. PTX did not affect intradermal skin test reactivity to house dust mites after 15 min.
Descriptors: atopy, pentoxifylline, hypersensitivity, tumour necrosis factor, interleukin 6,

cytokines.
Language of Text: , LS=German; Spanish; French.

Mirsalis, J.C., J. Schindler Horvat, J.R. Hill, C.E. Green, C. Mitoma, J.E. Tomaszewski, C.A. Tyson, and S.J. Donohue (2003). **Toxicity of a quinocarmycin analog, dx-52-1, in rats and dogs in relation to clinical outcome.** *Cancer Chemotherapy and Pharmacology* 51(3): 193-201. ISSN: 0344-5704.
NAL Call Number: RC271.C5C28
Abstract: Purpose: Quinocarmycin analog DX-52-1 is a cyanated derivative of quinocarmycin, a compound isolated from cultures of Streptomyces melanovinaceus. DX-52-1 was selected for preclinical development because it showed efficacy against melanoma cell lines in the NCI human tumor cell screen and melanoma xenografts in mice. This report describes studies in rats and dogs to determine the maximum tolerated dose (MTD) and identify dose-limiting toxicities (DLT) in each species in different regimens to establish a safe starting dose and potential target organs of DX-52-1 for phase I clinical trials. Methods: DX-52-1 was administered to Fischer 344 rats using repeated intravenous (i.v.) slow bolus injections following q3hX3 and q3hX3,q7dX3 regimens, and to beagle dogs using a single injection, 6-h continuous i.v. infusion (c.i.v.) and weekly 6-h c.i.v. for 3 weeks. Endpoints evaluated included clinical observations, body weights, hematology, serum clinical chemistry, and microscopic pathology of tissues. Results: The MTD of DX-52-1 was a total dose of 18 mg/m2 body surface area for q3hX3 administration in rats and 30 mg/m2 for a single c.i.v. administration in dogs. The total dose MTD for rats on a weekly (q3hX3,q7dX3) regimen was 54 mg/m2, and for dogs on the weekly X3 (6-h c.i.v.) infusion was 60 mg/m2. In rats, significant elevations in blood urea nitrogen and creatinine were observed together with acute renal tubular necrosis histologically. Modest increases in liver enzymes were also observed, as were decreases in reticulocytes that were unaccompanied by histologic changes in liver and bone marrow. In dogs, adverse signs included vomiting/retching, diarrhea, and transient hypothermia; also red blood cells, hemoglobin, hematocrit, and lymphocytes were decreased. Histologic evaluation of tissues from dogs revealed necrosis and cellular depletion of the bone marrow, and extensive damage to the entire gastrointestinal tract, including marked cellular necrosis of the mucosa and lymphoid necrosis of the gastrointestinal associated lymphoid tissue. Destruction of the mucosal lining of the intestinal tract was likely responsible for dehydration, toxemia, septicemia, and shock seen in moribund dogs. Conclusions: The MTD values were comparable between rats and dogs given roughly similar dose regimens (single dose or weekly) and both species tolerated a higher total dose with weekly administration. However, the principal target organ responsible for DLT in rats was the kidney, whereas in dogs, the most severe effects were on the gastrointestinal tract and bone marrow. Both renal and gastrointestinal toxicities were reported in patients after 6-h c.i.v. infusions in a limited phase I clinical trial, indicating that neither animal model alone was predictive of DX-52-1-induced toxicity in humans, and that both species were required to define human toxicity.
Descriptors: animal models, rats, dogs, human, cancer therapy, melanoma, toxicity studies, preclinical development, Quinocarmycin analog DX-52-1, efficacy pharmacology, toxicology, bone marrow toxicity, blood and lymphatic disease, gastrointestinal toxicity, digestive system

disease, renal toxicity, toxicity, urologic disease, histopathology, histology and cytology techniques, laboratory techniques, body weight, species differences.

Modiano, J.F., S.P. Fosmire, S.R. Bianco, R. Thomas, M. Breen, D.M. Getzy, J. Wojcieszyn, and S.C. Helfand (2003). **Differential phosphorylation of rb in canine b and t cell lymphomas.** *FASEB Journal* 17(7): C324-C325. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: tumor biology, B cell lymphoma, blood and lymphatic disease, immune system disease, neoplastic disease, T cell lymphoma, blood and lymphatic disease, neoplastic disease, immunohistology, immunologic techniques, laboratory techniques.

Moore, R.B., Z. Xiao, R.J. Owen, R. Ashforth, D. Dickey, C. Helps, and J. Tulip (2008). **Photodynamic therapy of the canine prostate: intra-arterial drug delivery.** *Cardiovascular and Interventional Radiology* 31(1): 164-76.
NAL Call Number: RC683.5.R3
Abstract: PURPOSE: Interstitial photodynamic therapy (PDT) selectively destroys tissue targeted with a photosensitizer and then exposed to light of a specific wavelength. We report a novel delivery method--intra-arterial drug delivery for PDT of the prostate--in a canine model. METHODS: To evaluate drug distribution, the prostatovesical artery was selectively cannulated and photosensitizers alone or in conjunction with 99m-technetium-labeled macro-aggregated albumin ((99m)Tc-MAA) were injected via a 3 Fr microcatheter in 8 animals. One dog was followed for 3 months to determine tolerance and toxicity. The remaining animals were euthanized and imaged with whole-body single photon emission CT and gamma counting for radioactivity distribution. Photosensitizer distribution was further analyzed by fluorescence confocal microscopy and tissue chemical extraction. To evaluate PDT, the photosensitizer QLT0074 was infused in 3 animals followed by interstitial illumination with 690 nm laser light. RESULTS: Intra-arterial infusion selectively delivered drugs to the prostate, with both radioactivity and photosensitizer levels significantly higher (up to 18 times) than in the surrounding organs (i.e., rectum). With unilateral injection of (99m) Tc-MAA, only the injected half of the prostate showed activity whereas bilateral administration resulted in drug delivery to the entire prostate. PDT resulted in comprehensive damage to the prostate without severe complications or systemic toxicity. CONCLUSION: Injection of radiolabeled MAA into the prostatovesical artery results in distribution within the prostate with negligible amounts reaching the adjacent organs. PDT also demonstrates selective damage to the prostate, which warrants clinical application in targeted prostate therapies.
Descriptors: photochemotherapy methods, prostate drug effects, radiopharmaceuticals administration and dosage, technetium tc 99m aggregated albumin administration and dosage, dogs, fluoroscopy, follow up studies, indoles administration and dosage, indoles metabolism, indoles pharmacokinetics, infusions, intra arterial, microscopy, confocal methods, models, animal, organometallic compounds administration and dosage, organometallic compounds metabolism, organometallic compounds pharmacokinetics, photochemotherapy adverse effects, photosensitizing agents administration and dosage, photosensitizing agents metabolism, photosensitizing agents pharmacokinetics, porphyrins administration and dosage, porphyrins metabolism, prostate metabolism, prostate radiography, radiopharmaceuticals adverse effects, radiopharmaceuticals pharmacokinet-

ics, technetium tc 99m aggregated albumin adverse effects, technetium tc 99m aggregated albumin pharmacokinetics, tissue distribution, tomography, emission computed, single photon.

Ong, A.M., L.M. Su, I. Varkarakis, T. Inagaki, R.E. Link, S.B. Bhayani, A. Patriciu, B. Crain, and P.C. Walsh (2004). **Nerve sparing radical prostatectomy: effects of hemostatic energy sources on the recovery of cavernous nerve function in a canine model.** *Journal of Urology* 171(4 Supplement): 284. ISSN: 0022-5347.
NAL Call Number: 448.8 J8234
Descriptors: methods and techniques, reproductive system, reproduction, bipolar electrosurgery, experimental surgical techniques, laboratory techniques, nerve sparing radical prostatectomy, cavernous nerve function, erectile function, hemostatic energy source, peak intracavernous pressure.

Pinho, S.S., A.J. Matos, C. Lopes, N.T. Marcos, J. Carvalheira, C.A. Reis, and F. Gartner (2007). **Sialyl Lewis x expression in canine malignant mammary tumours: correlation with clinicopathological features and E-Cadherin expression.** *BMC Cancer* 7: 124.
Abstract: BACKGROUND: Sialyl Lewis x (sLex) antigen is a carbohydrate antigen that is considered not only a marker for cancer but also implicated functionally in the malignant behaviour of cancer cells. Overexpression of sLex is associated with enhanced progression and metastases of many types of cancer including those of the mammary gland. Canine mammary tumours can invade and give rise to metastases via either lymphatic or blood vessels.E-Cadherin is specifically involved in epithelial cell-to-cell adhesion. In cancer, E-Cadherin underexpression is one of the alterations that characterizes the invasive phenotype and is considered an invasion/tumour suppressor gene. Partial or complete loss of E-Cadherin expression correlates with poor prognosis in canine malignant mammary cancer. The aim of this study was to analyse the sLex expression in canine malignant mammary tumours and to evaluate if the presence of sLex correlates with the expression of E-Cadherin and with clinicopathological features. METHODS: Fifty-three cases of canine mammary carcinomas were analysed immunohistochemically using monoclonal antibodies against sLex (IgM) and E-Cadherin (IgG). The clinicopathological data were then assessed to determine whether there was a correlation with sLex tumour expression. Double labelled immunofluorescence staining was performed to analyse the combined expression of sLex and E-Cadherin. RESULTS: sLex expression was consistently demonstrated in all cases of canine mammary carcinomas with different levels of expression. We found a significant relationship between the levels of sLex expression and the presence of lymph node metastases. We also demonstrated that when E-Cadherin expression was increased sLex was reduced and vice-versa. The combined analysis of both adhesion molecules revealed an inverse relationship. CONCLUSION: In the present study we demonstrate the importance of sLex in the malignant phenotype of canine malignant mammary tumours. Our results support the use of sLex as a prognostic tumour marker in canine mammary carcinomas. Furthermore, we showed that sLex and E-Cadherin expression were inversely correlated. Future studies are warranted to clarify the molecular mechanism underlying the relation between sLex and E-Cadherin in canine mammary carcinoma cells which represents an important comparative model to woman breast cancer.

Descriptors: cadherins metabolism, mammary neoplasms, animal metabolism, mammary neoplasms, animal pathology, neoplasm invasiveness pathology, oligosaccharides metabolism, tumor markers, biological analysis, biopsy, needle, cadherins genetics, cell transformation, neoplastic pathology, dogs, gene expression regulation, neoplastic, immunohistochemistry, mammary neoplasms, animal genetics, models, animal, neoplasm staging, oligosaccharides genetics, probability, random allocation, reference values, sensitivity and specificity, tumor markers, biological genetics.

Sfacteria, A., C. Bertani, G. Costantino, M.d. Bue, M. Paiardini, B. Cervasi, A. Piedimonte, and G.d. Vico (2003). **Cyclin D1 expression in pre-cancerous and cancerous lesions of the canine mammary gland**. *Journal of Comparative Pathology.* 128(4): 245-251. ISSN: 0021-9975.
NAL Call Number: 41.8 J82
Abstract: Overexpression of cyclin D1, the regulatory subunit of cyclin-dependent kinases (cdk4 and cdk6) involved in cell cycle control, is often found in breast cancer and other types of human cancer. Increased expression, or stability of cyclin D1 molecules may cause sufficient cdk4 activation to produce retinoblastoma protein phosphorylation independently of mitogenic signals; this results in commitment of cells to the G1 phase at mitosis. In the present study, cyclin D1 expression was investigated in pre-cancerous and cancerous lesions of the canine mammary gland by a complex experimental approach which included Western blot and immunohistochemical analysis of cyclin D1 and the related molecular system. Furthermore, to define relationships between cell growth and expression of cyclin D1, proliferative activity was studied by the AgNOR technique. The study provided the following information. Cyclin D1 overexpression was largely independent of the type of proliferative anomaly. Indeed, cyclin D1 was expressed in 60% of the pre-cancerous lesions and in 44% of cancerous lesions. Mitotic activity and cyclin D1 expression were related: mammary lesions that expressed cyclin D1 showed a high proliferative ratio, the opposite being true of cyclin D1-negative cell populations. This study may contribute to the establishment of an animal model for anti-cancer research based on cyclin D1 suppression or cdk inactivation, or both.
Descriptors: animal model, breast cancer, bitches, kinases, mammary gland diseases, mammary glands, mitosis, neoplasms, pathology, phosphorylation.

Spugnini, E.P., I. Dotsinsky, N. Mudrov, G. Cardosi, G. Citro, A. D'Avino, and A. Baldi (2007). **Biphasic pulses enhance bleomycin efficacy in a spontaneous canine perianal tumors model.** *Journal of Experimental and Clinical Cancer Research CR* 26(4): 483-7. ISSN: 0392-9078.
Abstract: Perianal tumors (adenoma and carcinoma of the hepatoid glands) are frequently reported in veterinary literature. They are locally aggressive tumors with a low tendency to metastatic spread. An hormonal ethiology has been identified for the development of perianal adenomas in male dogs, while the carcinomas are free from hormonal influence. Standard treatments include surgery, cryotherapy or, in selected cases, radiation therapy. In this article we describe the outcome of a small cohort of canine patients with perianal tumors treated with bleomycin selectively driven by trains of biphasic pulses (electrochemotherapy). Twelve canine patients, eight with adenoma and four with carcinoma of the perianal glands, entered the study and received two sessions of ECT under sedation. The pets had local injection ofbleomycin at the concentration of 1.5 mg/mg and five minutes after the chemotherapy, trains

of 8 biphasic electric pulses lasting 50 + 50 micros each, with 1 ms interpulse intervals, were delivered by means of modified caliper and needle array electrodes or, for difficult districts, through paired needle electrode. The overall response rate was 91% with a 83% of complete response (10/12); one dog had a PR that lasted 12 months and another had progressive disease. Electrochemotherapy appears as a safe and efficacious modality for the treatment of perianal tumors and warrants further investigations.
Descriptors: anal gland neoplasms drug therapy, antibiotics, antineoplastic analysis, bleomycin analysis, dog diseases drug therapy, electrochemotherapy methods, antibiotics, antineoplastic therapeutic use, bleomycin therapeutic use, combined modality therapy, dogs, models, animal.

Suami, H., J.K. O'Neill, W.R. Pan, and G.I. Taylor (2008). **Perforating lymph vessels in the canine torso: direct lymph pathway from skin to the deep lymphatics.** *Plastic and Reconstructive Surgery* 121(1): 31-6.
Abstract: BACKGROUND: Classic anatomical lymphatic mapping in humans is represented by four territories in the torso divided by the midline and horizontal line at the L2 level. Each territory drains into the ipsilateral axillary or inguinal lymph nodes. Recently, preoperative lymphoscintigraphy for staging breast cancer and malignant melanoma has become common in the clinical arena. It reveals an undescribed direct pathway from the skin of the loin to intraabdominal lymph nodes. The authors investigated the presence of such a lymphatic route using a dog model. METHODS: The authors used seven greyhound dogs for this study. The caliber of their lymph vessels was similar to those of humans, and because of a lack of fat tissue under the integument, the vessels were identified easily. The authors applied their original radiographic technique using hydrogen peroxide and lead oxide for delineating the superficial lymphatic system. RESULTS: Lymphatic territories of the torso were classified with relation to their regional lymph nodes. The authors found perforating lymph vessels in the lumbar and gluteal regions. They originated from the skin, penetrated the abdominal wall, and then drained into paraaortic lymph nodes instead of the axillary and inguinal lymph nodes. They were always accompanied by blood vessels, especially perforating veins. CONCLUSIONS: The authors found perforating lymph vessels in a canine torso. They seem to be equivalent to the unexpected lymph pathways found in humans using lymphoscintigraphy.
Descriptors: abdomen anatomy and histology, lymphatic vessels anatomy and histology, lymphatic vessels radiography, skin anatomy and histology, cadaver, dogs, lymphography, models, animal.

Sun, H., J.M. Collins, T.J. Mangner, O. Muzik, and A.F. Shields (2003). **Imaging (18f)fau (1-(2'-deoxy-2'-fluoro-beta-d-arabinofuranosyl) uracil) in dogs.** *Nuclear Medicine and Biology* 30(1): 25-30. ISSN: 0969-8051.
Abstract: We have studied the biodistribution of (18F)FAU ((1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)uracil), which previous work has shown is incorporated into DNA and functions as an inhibitor of DNA synthesis. It is being tested as a potential antineoplastic agent and imaging agent for PET. We have produced (18F)FAU and injected the tracer into 3 normal dogs and imaged them for up to 4 hours and removed tissues along with blood and urine samples for HPLC and activity analysis. The results showed that (18F)FAU evenly dis-

tributed to most of organs. In sharp contrast to our prior experience with thymidine and its analogs, marrow had less retention of (18F)FAU than the non-proliferating tissues.
Descriptors: radiation biology, tumor biology, cancer, neoplastic disease, diagnosis, positron emission tomography, diagnostic techniques, imaging and microscopy techniques, laboratory techniques.

Sun, S., S. Wang, N. Ge, T. Lei, Q. Lu, Z. Zhou, A. Yang, Z. Wang, and M. Sun (2007). **Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model.** *Endoscopy* 39(6): 530-4.
Abstract: BACKGROUND AND STUDY AIM: Interstitial chemotherapy using surgically implanted, biodegradable polymers has been reported. Our aim in this study was to investigate the feasibility and safety of endoscopic ultrasound- (EUS-) guided interstitial chemotherapy of the pancreas in a canine model. MATERIALS AND METHODS: A therapeutic 19-gauge needle with a large channel was inserted into the pancreas under EUS guidance. The polymers for sustained intratumoral release of 5-fluorouracil were implanted into the tissue by the needle. After 14 days of clinical observation, the animals were sacrificed and the tissue response to the local chemotherapy was examined. RESULTS: All the polymers were implanted successfully and no implant migration occurred. Localized tissue fibrous necrosis was achieved in the pancreas, without significant complications. The apoptotic index of the tissue within 1 cm of the focus increased. Biochemical parameters were normal in all the dogs. CONCLUSIONS: EUS-guided implantation of polymers is a safe, simple, and minimally invasive technique for interstitial chemotherapy in the pancreas.
Descriptors: antimetabolites, antineoplastic administration and dosage, endosonography, fluorouracil administration and dosage, pancreas ultrasonography, dogs, feasibility studies, injections, intralesional, models, animal, pancreas pathology, polymers administration and dosage.

Wu Jian Hui , Sun Zu Yue , Zhong En Hong , Zhu Yan , Liu Gui Ming , He Gui Lin , and Cao Lin (2003). **Pathology changes of vas deferens in benign prostatic hyperplasia model of beagle dogs.** *Zhongguo Yaolixue Yu Dulixue Zazhi* 17(3): 221-226. ISSN: 1000-3002.
Abstract: AIM: The objective of this investigation was to research the proliferation mechanism of vas deferens in benign prostatic hyperplasia. METHODS: The vas deferens, from beagle dogs which have been administered testosterone propionate(TP) to build benign prostatic hyperplasia model in vivo, was analyzed by a series of methods. Dihydrotestosterone (DHT) in vas deferens was detected by radioimmunoassay, the slices (4 mum) of vas deferens were stained with HE, and the duct area as well as the height of epithelial cell were measured with videodensitometer. The apoptosis rate was determined by flow cytometry method. The expression of prostatic specific antigen (PSA), prostatic acid phosphatase (PAP), Bcl-2 and P53 were determined by immunohistochemical methods. The nucleosomal DNA fragmentation was monitored by agarose gel electrophoresis. RESULTS: DHT level of vas deferens was increased with increasing TP doses, but there was no significant difference between groups. After being administered TP, the duct area of vas deferens was enlarged (P<0.01), and the height of epithelial cell was increased (P<0.01). The cell apoptosis rate of control was higher than that of 0.8 and 7.5 mgcntdotkg-1 TP groups(P<0.01). While there were no differences in expression of PSA, PAP and Bcl-2 between control and other groups, the expression of

P53 of control was higher than that of the other groups(P<0.05). In agarose gel electrophoresis, the 200 bp base pair DNA fragments and the multiples of them were observed in control, while similar phenomenon didn't find in other groups. CONCLUSION: DHT induces vas deferens to proliferate, and the proliferation of vas deferens is related to inhibition of apoptosis.
Descriptors: endocrine system, chemical coordination and homeostasis, reproductive system, reproduction, tumor biology, benign prostatic hyperplasia, reproductive system disease, male, urologic disease, pathology changes, proliferation mechanism.
Language of Text: Chinese.

Zhang, J., X. Chen, M.S. Kent, C.O. Rodriguez, and X. Chen (2009). **Establishment of a dog model for the p53 family pathway and identification of a novel isoform of p21 cyclin-dependent kinase inhibitor.** *Molecular Cancer Research* 7(1): 67-78. ISSN: 1541-7786.
NAL Call Number: RC261.A1
Abstract: Spontaneous tumors in the dog offer a unique opportunity as models to study human cancer etiology and therapy. p53, the most commonly mutated gene in human cancers, is found to be altered in dog cancers. However, little is known about the role of p53 in dog tumorigenesis. Here, we found that on exposure to DNA damage agents or MDM2 inhibitor nutlin-3, canine p53 is accumulated and capable of inducing its target genes, MDM2 and p21. We also found that on DNA damage, canine p53 is accumulated in the nucleus, followed by MDM2 nuclear translocation and increased 53BP1 foci formation. In addition, we found that canine p63 and p73 are up-regulated by DNA damage agents. Furthermore, colony formation assay showed that canine tumor cells are sensitive to DNA damage agents and nutlin-3 in a p53-dependent manner. Surprisingly, canine p21 is expressed as two isoforms. Thus, we generated multiple canine p21 mutants and found that amino acids 129 to 142 are required, whereas amino acid 139 is one of the key determinants, for the expression of two p21 isoforms. Finally, we showed that although the full-length human p21 cDNA expresses one polypeptide, amino acid 139 seems to play a similar role as that in canine p21 for various migration patterns. Taken together, our results indicate that canine p53 family proteins have biological activities similar to human counterparts. These similarities make the dog an excellent outbred spontaneous tumor model, and the dog can serve as a translation model from benchtop to cage side and then to bedside.
Descriptors: cyclin dependent kinase inhibitor p21 genetics, tumor suppressor protein p53 physiology, amino acid sequence, antineoplastic agents pharmacology, bone neoplasms, camptothecin pharmacology, cell line, cell line, tumor, conserved sequence, cyclin dependent kinase inhibitor p21 chemistry, dna damage, dogs, doxorubicin pharmacology, kidney, melanoma, mice, models, animal, molecular sequence data, osteosarcoma, sequence alignment, sequence homology, amino acid.

Pharmacology

Albright, A.L. (2007). **Long-term intraventricular baclofen infusion in beagles.** *Journal of Neurosurgery* 107(3 Suppl): 225-7. ISSN: 0022-3085.

Abstract: OBJECT: This study was designed to evaluate the clinical and histopathological effects of long-term (3-month) intraventricular baclofen (IVB) infusion in beagle dogs. METHODS: Catheters were inserted stereotactically into the lateral ventricles of nine dogs and were connected to implanted Synchromed II pumps. Saline solution (control animals) and IVB (experimental animals) were infused continuously. The IVB dosages ranged from 100 to 1000 microg/day. RESULTS: An IVB infusion of 135 microg/day or less throughout a 3-month period was associated with no adverse side effects in any animal. Infusion of 150 microg/day produced overt seizures in one dog and produced adverse side effects in another; a reduction in the dosage given to these animals to 135 microg/day was tolerated with no adverse effects. Infusion of IVB at a dosage of 250, 500, or 1000 microg/day caused lethal toxicity within the first 4 days of infusion. Histopathological specimens obtained at necropsy revealed no ventricular or subependymal changes in animals receiving an IVB dosage of 135 microg/day or less. CONCLUSIONS: Intraventricular baclofen infusion in beagles has dose-related toxicity; however, no clinical or neurological toxicity was evidenced at clinically tolerated dosages (< or =135 microg/day) throughout 3 months of infusion.

Descriptors: baclofen toxicity, muscle relaxants, central toxicity, baclofen pharmacology, brain pathology, cerebrospinal fluid metabolism, dogs, dose response relationship, drug, fourth ventricle, infusion pumps, injections, intraventricular, injections, spinal, magnetic resonance imaging, models, animal, muscle relaxants, central pharmacology, time factors.

Notes: Comments: Comment In: J Neurosurg. 2007 Sep;107(3 Suppl):224; discussion 224.

Alkharfy, K.M., R.M. Khan, B.M. Al Hadiya, H.S. Abou Auda, and R.R. Abou Shaaban (2007). **Disposition of abouthiouzine: a novel antihyperthyroid drug.** *Biopharmaceutics and Drug Disposition* 28(3): 105-11. ISSN: 0142-2782.

Abstract: Abouthiouzine is a novel antithyroid agent with a profile of fewer reported adverse effects than other currently used drugs. The purpose of this current work was to explore, for the first time, the disposition of abouthiouzine following intravenous and oral administration using an animal model; also, to study its plasma protein binding properties. Abouthiouzine (2 mg/kg intravenously) was administered to healthy male Vole rabbits and Beagle dogs. A dose of 20 mg/kg of the drug was also given orally to another group of Beagle dogs. Abouthiouzine plasma concentrations were measured using an HPLC method, and its pharmacokinetic parameters were determined by non-compartmental analysis. Abouthiouzine plasma protein binding was determined using an ultrafiltration technique. The drug was quickly eliminated from the rabbit and dog systemic circulations with terminal half-lives (T(1/2 lambda)) of 0.7 h and 1.9 h, respectively. The calculated T(1/2 lambda) following the oral administration in dogs was 1.8 h. Total abouthiouzine clearance (CL) in rabbits was 7.84+/-0.87 ml/min/kg, and 4.03+/-0.83 ml/min/kg in dogs. The apparent volume of distribution at steady state (V(ss)) in rabbits and dogs was 360.09+/-63.41 ml/kg and

481.10+/-62.64 ml/kg, respectively. The absolute oral bioavailability in dogs was approximately 16%, which may indicate poor absorption characteristics of the pure drug and/or an extensive first past effect. Protein binding studies have demonstrated that abouthiouzine has moderate-to-high binding properties (approximately 63%-86%). Further studies are needed to evaluate the route of elimination of abouthiouzine in these animal models including any metabolite formation and the role of enterohepatic recycling in this process. Copyright (c) 2007 John Wiley & Sons, Ltd.
Descriptors: antithyroid agents pharmacokinetics, polyamines pharmacokinetics, pyridines pharmacokinetics, administration, oral, antithyroid agents administration and dosage, area under curve, biological availability, blood proteins metabolism, chromatography, high pressure liquid, dogs, drug evaluation, preclinical, injections, intravenous, models, animal, polyamines administration and dosage, protein binding, pyridines administration and dosage, rabbits, species specificity, tissue distribution, ultrafiltration.

Barros, G.A., M.E. Marques, and E.M. Ganem (2007). **The effects of intrathecal administration of betamethasone over the dogs' spinal cord and meninges.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(5): 361-5. ISSN: 0102-8650.
Abstract: PURPOSE: To determinate the potential clinical and histological changes due the injection of betamethasone, when administered into the canine intrathecal space. METHODS: Twenty one animals were included in a random and blind manner in the study. After general anesthesia, intrathecal puncture was performed and 1 ml of the random solution was injected. The G1 dogs received 0.9% saline solution, the G2 dogs received 1.75 mg betamethasone and the G3 dogs received 3.5 mg of betamethasone. The animals were clinically evaluated for 21 days and then sacrificed. The lumbar and sacral portions of the spinal cord were removed for light microscopy histological analyses. RESULTS: No clinical changes were observed in any of the animals included in this study. No histological changes were observed in G1 animals. Inflammatory infiltration was observed in two dogs, one in G2, another in G3. Hemorrhage and necrosis were also seen in the G2 dog which inflammatory infiltration was detected. In other two dogs, one from G2 and another from G3, there was discreet fibrosis and thickness of the arachnoid layer which was focal in one and diffuse in the other. CONCLUSION: Intrathecal administration of betamethasone caused histological changes in the spinal cord and meninges in some of the dogs involved in this study.
Descriptors: anti inflammatory agents adverse effects, betamethasone adverse effects, meninges drug effects, spinal cord drug effects, analysis of variance, anti inflammatory agents administration and dosage, betamethasone administration and dosage, dogs, fibrosis etiology, inflammation chemically induced, inflammation pathology, injections, spinal, meninges pathology, models, animal, necrosis etiology, random allocation, sodium chloride administration and dosage, spinal cord pathology, spinal puncture.

Bilotta, F., L. Agati, V. Fabbrini, G. Centola, and G. Rosa (2003). **Pulmonary transit of levovist(r): a transthoracic echocardiographic study.** *2003 Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, USA; October 11-15, 2003,*
Abstract: After intravenous injection in spontaneously breathing patients and anesthetized dogs, ultrasound contrast agents opacify the right ventricle, pass through the lungs, opacify

the left ventricle and depict systemic organ perfusion patterns. Contrast ultrasound based intraoperative organ-perfusion studies -- currently limited to intraarterial or intraaortic injection -- require an intravenous ultrasound contrast agent that passes through the lungs during mechanical ventilation in humans. Effective lung transit of ultrasound contrast agents during controlled mechanical ventilation is a prerequisite for ultrasound-based real time systemic organ perfusion studies (myocardium, kidneys, liver and brain) because it allows the contrast agent injected intravenously to reach the systemic circulation. Whether an ultrasound contrast agent passes the lungs during mechanical ventilation depends on many factors, including biochemical interactions with blood gasses, intravascular pressure and shell stability. Mechanical ventilation alters the physiology of the pulmonary microcirculation by increasing intrathoracic pressure and pulmonary vascular resistance. Levovist(R) (Schering AG, Berlin, Germany) is a galactose and palmitic based air-filled ultrasound contrast agent used for organ perfusion studies with intravenous injection in spontaneously breathing patients. In this study, we investigated whether Levovist(R) injected intravenously during intermittent positive pressure ventilation (IPPV) opacifies the right and left ventricular cavities after lung transit. With transthoracic echocardiography we measured the time in cardiac cycles (CC), for contrast to appear in the right ventricle and traverse the lungs; and the intensity of right and left ventricular cavity opacification (RVCO and LVCO). Twenty patients undergoing elective peripheral neurosurgical procedures were prospectively enrolled. All patients received intravenous Levovist(R) 1 g, during spontaneous breathing (baseline), 5 min after the beginning of IPPV, and 5 min and 30 min after extubation. Pulmonary transit time was constant: 7 +- 3 CC at baseline, 6 +- 2 CC during IPPV, and 8 +- 2 CC at 5 min and 7 +- 3 CC at 30 min after extubation. In all patients, each of the four contrast injections achieved high-grade RVCO and LVCO, and remained constant before, during IPPV and at 5 and 30 minutes after extubation. In this study, conducted in patients mechanically ventilated during general anesthesia for peripheral neurosurgical procedures, intravenous injection of Levovist(R) during IPPV opacified the right ventricular cavity, passed physiologically through the lungs and opacified the left ventricular cavity. It did so at an intensity equivalent to that when patients breathed spontaneously. During surgery, especially in high-risk patients, adequate organ blood flow is critical for normal cellular metabolism and tissue preservation. Because hypoperfusion often precedes and causes functional damage, early diagnosis of inadequate tissue perfusion could guide treatment to restore perfusion. In conclusion, Levovist(R) injected intravenously provides physiologic pulmonary capillary transit in patients undergoing peripheral neurosurgical procedures during mechanical ventilation. An ultrasound contrast agent with these properties might make real-time echographic evaluation of organ perfusion patterns possible in patients during IPPV. Anesthesiology 2003; 99: A168.
Descriptors: methods and techniques, pharmacology, surgery, medical sciences, contrast ultrasound, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, mechanical ventilation, therapeutic and prophylactic techniques, transthoracic echocardiography, cardiac cycles.

Brandt, K.D., G.N.J. Smith, and S.L. Myers (2004). **Hyaluronan injection affects neither osteoarthritis progression nor loading of the oa knee in dogs**. *Biorheology* 41(3-4): 493-502. ISSN: 0006-355X.

NAL Call Number: QH505.A1B5
Abstract: We previously reported that intraarticular injections of hyaluronan (HA), administered prophylactically to dogs in whom knee osteoarthritis had been induced by transection of the anterior cruicate ligament, did not significantly modify the intraarticular pathology but decreased the proteogylcan concentration of the articular cartilage by as much as 30%. Because the cartilage proteoglycan concentration is directly related to the stiffness of the tissue, these results raised the possibility that intraarticular HA therapy could exacerbate OA. In the present study, using a different HA formulation, with a longer interval between intraarticular HA injection and examination of joint tissues, we found that neither prophylactic nor therapeutic administration of HA had an effect on the severity of OA pathology, the magnitude of vertical ground reaction forces generated by the unstable hind limb (a surrogate for joint pain), or the cartilage proteoglycan concentration. The data suggest that the suppression of proteoglycan synthesis induced by HA is temporary and fully reversible and that HA injections do not result in overloading of the OA extremity. A significant correlation was noted between the severity of chondropathy and the magnitude of the vertical ground reaction forces generated by the unstable limb.
Descriptors: animal care, pharmacology, skeletal system, movement and support, osteoarthritis, joint disease.

Carballo Jane, E., L.S. Gerckens, S. Luell, A.S. Parlapiano, M. Wolff, S.L. Colletti, J.R. Tata, A.K. Taggart, M.G. Waters, J.G. Richman, M.E. McCann, and M.J. Forrest (2007). **Comparison of rat and dog models of vasodilatation and lipolysis for the calculation of a therapeutic index for GPR109A agonists.** *Journal of Pharmacological and Toxicological Methods* 56(3): 308-16. ISSN: 1056-8719.
NAL Call Number: QP901.J6
Abstract: INTRODUCTION: GPR109A is the receptor mediating both the antilipolytic and vasodilatory effects of nicotinic acid. In order to develop agonists for GPR109A with improved therapeutic indices we have sought to optimize animal models that evaluate both nicotinic acid-mediated inhibition of lipolysis and stimulation of vasodilatation. The rat and the dog have previously been used to study the antilipolytic effects of nicotinic acid, but no optimal vasodilatation model exits in either species. METHODS: We have developed a vasodilatation model in the rat that measures changes in ear perfusion using laser Doppler flowmetry. In the dog, we have developed a model of vasodilatation measuring changes in red color values in the ear, using a spectrocolorimeter. Effects of GPR109A agonists on lipolysis were measured in both species after oral dosing of compounds, and measuring plasma levels of free fatty acids. RESULTS: In both rat and dog, GPR109A agonists induce dose- and time-dependent vasodilatation, similar to that observed in humans. Vasodilatation is inhibited in both species with cyclooxygenase inhibitors or a specific DP1 receptor antagonist, indicating that, as in man, nicotinic acid-induced vasodilatation in rats and dogs is mainly mediated by the release of PGD(2). DISCUSSION: Our results show that both rat and dog are useful models for the characterization of GPR109A agonists. A therapeutic index for GPR109A agonists can be calculated in either species.
Descriptors: lipolysis drug effects, nicotinic agonists pharmacology, receptors, g protein coupled agonists, vasodilation drug effects, anti inflammatory agents, non steroidal adminis-

tration and dosage, anti inflammatory agents, non steroidal pharmacology, antilipemic agents administration and dosage, antilipemic agents pharmacology, dogs, dose response relationship, drug, drug evaluation, preclinical methods, drug monitoring methods, fatty acids, nonesterified blood, indomethacin administration and dosage, indomethacin pharmacology, inhibitory concentration 50, injections, subcutaneous, models, animal, niacin administration and dosage, niacin pharmacology, nicotinic agonists administration and dosage, pyrazines administration and dosage, pyrazines pharmacology, rats, rats, sprague dawley, receptors, nicotinic metabolism.

Chen, D., B. Jefferson, S.J. Harvey, K. Zheng, C.J. Gartley, R.M. Jacobs, and P.S. Thorner (2003). **Cyclosporine a slows the progressive renal disease of alport syndrome (x-linked hereditary nephritis): results from a canine model.** *Journal of the American Society of Nephrology* 14(3): 690-698. ISSN: 1046-6673.

Abstract: Alport syndrome refers to a hereditary disorder characterized by progressive renal disease and a multilaminar appearance to the glomerular basement membrane (GBM). In a small group of patients with Alport syndrome, cyclosporine A was reported to decrease proteinuria and maintain stable renal function over 7 to 10 yr of follow-up. The present study examined the effect of cyclosporine A on GBM structure and the progression to renal failure in a canine model of X-linked Alport syndrome. Affected male dogs and normal male dogs treated with cyclosporine A underwent serial renal biopsies. Body weight, serum concentrations of creatinine and albumin, and GFR were sequentially determined. Controls consisted of untreated dogs that developed end-stage renal failure by 8 mo of age. Renal biopsies were assessed for glomerulosclerosis and the percent of multilaminar GBM as measured by image analysis. Significant differences were found between treated and untreated affected dogs for weight, serum creatinine, and GFR. There was a significant delay in the progression of multilaminar change to the GBM, although treated affected dogs at termination had attained approximately 100% split GBM as did untreated affected dogs. A significant difference in the number of sclerotic glomeruli was also noted; treated dogs rarely developed obsolete glomeruli during the period studied. Interstitial fibrosis was not significantly affected by cyclosporine A treatment. These findings indicate that cyclosporine A is beneficial in slowing, but not stopping, the clinical and pathologic progression of Alport syndrome. At least part of this beneficial effect comes from a delayed deterioration of GBM structure, which in turn may be related to glomerular hemodynamics altered by cyclosporine A.

Descriptors: genetics, pharmacology, urinary system, chemical coordination and homeostasis, Alport syndrome, X linked hereditary nephritis, congenital disease, genetic disease, urologic disease, glomerulosclerosis, interstitial fibrosis, disease miscellaneous, renal disease, drug therapy, renal failure, image analysis, imaging and microscopy techniques, laboratory techniques, renal biopsy, glomerular filtration rate, body weight, glomerular hemodynamics.

Cho, S., S. Zhang, H. Ureshino, T. Hara, S. Tomiyasu, and K. Sumikawa (2003). **Hemodynamic interactions of propofol and dantrolene in chronically instrumented dogs.** *Anesthesia and Analgesia* 96(5): 1369-1373. ISSN: 0003-2999.

Abstract: The hemodynamic interaction of dantrolene, a specific drug for malignant hyperthermia, and propofol which appears to be safe in malignant hyperthermia-susceptible

patients, has not been investigated. We performed this study to examine the hemodynamic actions of dantrolene at a therapeutic dose during propofol anesthesia. Ten dogs were chronically instrumented for the measurements of systemic and coronary hemodynamics. The dogs were assigned to receive propofol with vehicle or dantrolene in a random manner on separate experimental days. Propofol significantly decreased mean arterial blood pressure, left ventricular systolic and end-diastolic pressure, the maximal rate of increase in left ventricular pressure, and left ventricular regional segment shortening. Coronary blood flow (CBF) was unchanged but coronary vascular resistance (CVR) decreased. Dantrolene reversed the decrease in mean arterial blood pressure and left ventricular systolic pressure caused by propofol, and significantly increased heart rate. However, left ventricular end-diastolic pressure, cardiac output, maximal rate of increase in left ventricular pressure, and segment shortening were unchanged. CBF was significantly increased with a decrease in CVR. These results suggest that dantrolene reverses the hypotensive action produced by propofol and causes an increase in CBF with a decrease in CVR, but does not significantly change the negative inotropic effects. Thus, dantrolene exerts favorable hemodynamic effects during propofol anesthesia.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, pharmacology, malignant hyperthermia, metabolic disease, muscle disease, drug induced, cardiac output, coronary blood flow, drug drug interaction, mean arterial blood pressure.

Coleman, K.M., R. Voigts, D.P. DeVore, P. Termin, and W.P.3. Coleman (2008). **Neocollagenesis after injection of calcium hydroxylapatite composition in a canine model.** *Dermatologic Surgery Official Publication for American Society for Dermatologic Surgery [Et Al.]* 34(Suppl 1): S53-5.
Descriptors: biocompatible materials pharmacology, collagen metabolism, durapatite pharmacology, skin drug effects, cosmetic techniques, dogs, injections, intradermal, injections, subcutaneous, models, animal, photometry, pilot projects, skin metabolism, skin pathology, time factors.

Critchley, L., B. Ding, B. Fok, D. Wang, B. Tomlinson, A. James, G.N. Thomas, and J. Critchley (2004). **The effects of candesartan and ramipril on adrenal catecholamine release in anaesthetized dogs**. *European Journal of Pharmacology* 489(1-2): 67-75. ISSN: 0014-2999.
NAL Call Number: QP901.E8
Descriptors: angiotensin II type 1 receptor antagonist, angiotensin II converting enzyme inhibitor ramipril, endocrine system, chemical coordination and homeostasis, pharmacology, blood pressure.

Crystal, G.J., M. El Orbany, X. Zhou, M.R. Salem, and S.J. Kim (2008). **Hemodilution does not alter the coronary vasodilating effects of endogenous or exogenous nitric oxide.** *Canadian Journal of Anaesthesia; Journal Canadien D'Anesthesie* 55(8): 507-14. ISSN: 0832-610X.
Abstract: Introduction: It is well known that hemoglobin is a scavenger of nitric oxide (NO). The present study used a canine model to test the hypothesis that acute normovolemic hemodilution (ANH) affects NO-mediated coronary vasodilation. METHODS: Studies were performed in 18 open-chest, anesthetized dogs. In Series 1, the contribution of

endogenous NO to coronary vasodilatation during ANH with 5% dextran-40 (reduction in hematocrit by 50%) was assessed. This was accomplished by comparing myocardial blood flow (MBF; radioactive microspheres) in the left anterior descending (LAD) region, which was treated with the NO synthase inhibitor, N(G)-nitro-L-arginine methyl ester (L-NAME), to that in the circumflex (control) region. In Series 2, the LAD was perfused via a controlled-pressure extracorporeal system with coronary blood flow (CBF) measured with an ultrasonic, transit-time flow transducer. The dose-dependent increases in CBF caused by acetylcholine (ACh), which releases endogenous NO from the vascular endothelium, and sodium nitroprusside (SNP), which provides exogenous NO, were compared before and during ANH. RESULTS: Acute normovolemic hemodilution caused similar (approximately twofold) increases in MBF ($P < 0.01$) in the absence and presence of L-NAME, and it did not affect the dose-related increases in CBF caused by ACh and SNP. CONCLUSIONS: Series 1: under baseline conditions, hemoglobin in red blood cells does not limit the coronary vasodilatation resulting from tonic release of NO; NO does not mediate coronary vasodilation during ANH. Series 2: ANH does not influence the coronary vasodilating effects of increased levels of NO, whether due to endogenous release (ACh) or infusion of an NO donor (SNP).
Descriptors: coronary vessels drug effects, hemodilution adverse effects, nitric oxide pharmacology, nitric oxide physiology, nitric oxide synthase antagonists and inhibitors, acetylcholine pharmacology, adenosine pharmacology, blood gas analysis, blood pressure drug effects, coronary vessels radionuclide imaging, dogs, enzyme inhibitors pharmacology, free radical scavengers pharmacology, heart rate drug effects, hemodilution methods, models, animal, ng nitroarginine methyl ester pharmacology, nitroprusside pharmacology, treatment outcome, vasodilator agents pharmacology.

Dane, D.M., X. Yan, R.M. Tamhane, R.L.J. Johnson, A.S. Estrera, D.C. Hogg, R.T. Hogg, and C.C.W. Hsia (2004). **Retinoic acid-induced alveolar cellular growth does not, improve function after right pneumonectomy.** *Journal of Applied Physiology* 96(3): 1090-1096. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: To determine whether all-trans retinoic acid (RA) treatment enhances lung function during compensatory lung growth in fully mature animals, adult male dogs (n=4) received 2 mgcntdotkg-1cntdotday-1 po RA 4 days/wk beginning the day after right pneumonectomy (R-PNX, 55-58% resection). Litter-matched male R-PNX controls (n=4) received placebo. After 3 mo, transpulmonary pressure (TPP)-lung volume relationship, diffusing capacities for carbon monoxide and nitric oxide, cardiac output, and septal volume (Vtiss-RB) were measured under anesthesia by a rebreathing technique at two lung volumes. Lung air and tissue volumes (Vair-CT and Vtiss-CT) were also measured from high-resolution computerized tomographic (CT) scans at a constant TPP. In RA-treated dogs compared with controls, TPP-lung volume relationships were similar. Diffusing capacities for carbon monoxide and nitric oxide were significantly impaired at a lower lung volume but similar at a high lung volume. Whereas Vtiss-RB was significantly lower at both lung volumes in RA-treated animals, Vair-CT and Vtiss-CT were not different between groups; results suggest uneven distribution of ventilation consistent with distortion of alveolar geometry and/or altered small airway function induced by RA. We conclude that RA does not improve resting pulmonary function during the early months after R-PNX despite histological evidence of its

action in enhancing alveolar cellular growth in the remaining lung.
Descriptors: methods and techniques, pharmacology, respiratory system, respiration, right pneumonectomy, experimental surgical techniques, laboratory techniques, alveolar cellular growth, cardiac output, diffusing capacity for carbon monoxide, lung air, lung function, lung volume, resting pulmonary function, septal volume, tissue volume, transpulmonary pressure.

Dias Junior, C.A., J.T. Sertorio, and J.E. Tanus Santos (2007). **Aminoguanidine produces beneficial haemodynamic effects in a canine model of acute pulmonary thromboembolism.** *Acta Physiologica Oxford, England* 191(3): 189-96. ISSN: 1748-1708.
NAL Call Number: QP1 .A2
Abstract: AIM: Activating the nitric oxide (NO)-cyclic guanosine 3',5'-monophosphate (cGMP) pathway improves haemodynamics following acute pulmonary thromboembolism (APT). However, the role of NO synthase (NOS) isoforms in the responses to APT has not been determined. We examined the effects of selective and non-selective inducible NOS (iNOS) inhibition. METHODS: Haemodynamic evaluations were performed in non-embolized dogs treated with saline (control group; n = 4), L-NAME (NAME group; n = 3), or aminoguanidine (AG group; n = 3), and in dogs that received the same drugs and were embolized with 5 mL kg(-1) of clots made with autologous blood (Emb group, n = 9; NAME + Emb group, n = 4 and AG + Emb group, n = 7). The lung concentrations of nitrite/nitrate (NOx) and cGMP were determined by chemiluminescence and ELISA respectively. RESULTS: Acute pulmonary thromboembolism increased mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance index (PVRI) by 21.4 +/- 1.7 mmHg and by 843 +/- 34 dyn s cm(-5) m(-2), respectively, in Emb group. MPAP and PVRI increased to higher levels in the NAME + Emb group 15 min after APT and all dogs in this group died 15-30 min after APT. Conversely, lower MPAP and PVRI levels were found in the AG + Emb group 2 h after APT compared with the Emb group (both $P < 0.05$). Higher NOx concentrations were found in the Emb group compared with the other groups (all $P < 0.05$). Higher cGMP concentrations were found in the Emb and AG + Emb groups compared with the other groups (all $P < 0.05$). CONCLUSIONS: These results indicate that endogenous NO protects against APT-induced cardiovascular responses. Moreover, iNOS-derived NO possibly produces unfavourable effects, which are counteracted by aminoguanidine. However, non-NO-related mechanisms may also be involved.
Descriptors: guanidines therapeutic use, nitric oxide synthase type ii antagonists and inhibitors, pulmonary embolism drug therapy, acute disease, blood pressure drug effects, cyclic gmp analysis, cyclic gmp metabolism, dogs, lung chemistry, lung metabolism, models, animal, ng nitroarginine methyl ester metabolism, ng nitroarginine methyl ester therapeutic use, nitrates analysis, nitrates metabolism, nitric oxide metabolism, nitric oxide synthase type ii metabolism, pulmonary embolism metabolism, vascular resistance drug effects.

Dong, M.S., Y. Sonoda, H. Konomi, M. Kawamoto, T. Takeda, and M. Tanaka (2003). **Total duodenectomy: effects of choecystokinin on the sphincter of oddi motility in conscious dogs.** *Digestive Disease Week Abstracts and Itinerary Planner*: Abstract No. S1160.
Abstract: Objective: Cholecystokinin(CCK) is an important gastrointestinal hormone controlling of the Sphincter of Oddi (SO) motility. The mechanism of CCK action on SO motility is not completely understood. Anatomical and electrophysiological studies suggested

direct duodenal neural projections to the SO. However the CCK action via duodeno-SO neural projections under physiological intact animal model has not been reported. The aim of this study is to determine the SO motility response to the CCK via the duodeno-SO neural projections using duodenectomized dogs. Methods: In control group (N=6), Thomas cannula was implanted into the duodenum. In duodenectomy group (N=6), the papilla was sutured to the jejunum and a Thomas cannula implanted opposite to the implanted papilla. In both groups, changes in the SO motility was recorded after intravenous injection of cholecystokinin-octapeptide (20 or 100ng/kg). Results: Injection of 20ng/kg CCK produced initial relaxation followed by contraction in control and no changes in duodenectomy. Injecting of 100ng/kg CCK produced a marked but brief contraction followed by relaxation in controls and only contraction after duodenectomy. Conclusions: (1) Response of SO induced by 20ng/kg CCK was mediated via CCK receptor on the duodenum. (2) The duodenal CCK receptor may be more sensitive to CCK than SO receptor..
Descriptors: digestive system, ingestion and assimilation, methods and techniques, pharmacology, total duodenectomy, clinical techniques, therapeutic and prophylactic techniques, sphincter motility, modulation .

Efrati, O., A. Barak, R. Ben Abraham, D. Modan Moses, M. Berkovitch, Y. Manisterski, D. Lotan, Z. Barzilay, and G. Paret (2003). **Should vasopressin replace adrenaline for endotracheal drug administration?** *Critical Care Medicine.* 31(2): 572-576. ISSN: 0090-3493.
Abstract: OBJECTIVE: Arginine vasopressin was established recently as a drug of choice in the treatment of cardiac arrest and in retractable ventricular fibrillation; however, the hemodynamic effect of vasopressin following endotracheal drug administration has not been fully elucidated. We compared the effects of endotracheally administered vasopressin vs. adrenaline on hemodynamic variables in a canine model, and we investigated whether vasopressin produces the same deleterious immediate blood pressure decrease as did endotracheal adrenaline in the canine model. DESIGN: Prospective controlled study. SETTING: Animal laboratory in Tel-Aviv University, Israel. SUBJECTS: Five adult mongrel dogs weighing 6.5-20 kg. INTERVENTIONS: Dogs were anesthetized; each dog was intubated orally, and both femoral arteries were cannulated for the measurement of arterial pressure and for sampling blood gases. Each dog was studied four times, 1 wk apart, by using the same protocol for injection and anesthesia: endotracheal placebo (10 mL NaCl 0.9%,), endotracheal vasopressin (1 units/kg), endobronchial adrenaline (0.1 mg/kg), and endotracheal adrenaline (0.1 mg/kg). Following placebo, vasopressin, and adrenaline instillation, five forced manual ventilations were delivered with an Ambu bag. Each dog was its own control. MEASUREMENTS AND MAIN RESULTS: Following placebo or drug administration, heart electrocardiography and arterial pressures were continuously monitored with a polygraph recorder for 1 hr. Endotracheal vasopressin produced an immediate increase of diastolic blood pressure (from 83 +/- 10 mm Hg [baseline] to 110 +/- 5 mm Hg at 1 min postinjection). This response lasted >1 hr. In contrast, both endotracheal and endobronchial administration of adrenaline produced an early and significant ($p < .05$) decrease in diastolic and mean blood pressures. The diastolic blood pressure increase from 85 +/- 10 mm Hg to 110 +/- 10 mm Hg took an ill-afforded 55 secs following endotracheal adrenaline. Diastolic blood pressure was significantly ($p < .05$) higher following vasopressin compared with adrenaline administration in both routes. CONCLUSIONS: Vasopressin accomplishes its hemodynamic effect,

particularly on diastolic blood pressure, more rapidly, vigorously, and protractedly and to a significant degree compared with both endotracheal and endobronchial adrenaline. Evaluation of the effects of endotracheal vasopressin in a closed chest cardiopulmonary resuscitation model is recommended.
Descriptors: intubation, femoral artery cannulation, vasopressin, henodynamic effect, diastolic blood pressure.

Ensminger, W., J. Knol, S. Deremer, E. Wilkinson, S. Walker, D. Williams, and J. Maybaum (2004). **Effects of dexamethasone or celecoxib on biliary toxicity after hepatic arterial infusion of 5-fluorodeoxyuridine in a canine model.** *Cancer Research* 64(1): 311-315. ISSN: 0008-5472.
NAL Call Number: 448.8 C16
Abstract: Previous work has shown that in humans the dose-limiting toxicity for fluorodeoxyuridine (2-fluoro-5'-deoxyuridine (FdUrd)) when administered by hepatic arterial infusion is biliary sclerosis. The current study was undertaken to attempt to modify this toxicity in a canine model that has been demonstrated to closely mimic the clinical situation. Unlike previous studies using this model, in which animals were sacrificed after extensive fibrosis had already occurred, the current experiments were designed so that observations of pathology were made at an earlier time, when the initial inflammatory injury underlying the fibrotic process was still taking place. Implantable pumps were used to deliver FdUrd into the hepatic artery of animals at a rate of 0.3 mg/kg/day in the presence or absence of 10 mg/week dexamethasone or 100 mg/day of celecoxib for 35 days, at which time the animals were beginning to show signs of toxicity. After evaluation for radiological evidence of biliary obstruction, the animals were sacrificed and portions of their livers were processed for examination of microscopic pathology and 2-bromo-5'deoxyuridine labeling index. Dexamethasone treatment protected the animals from biliary sclerosis determined radiologically, further validating this model as being representative of the response in humans. Similarly the Cox-2 inhibitor, celecoxib, appeared to provide protection against radiological changes of biliary stricture, although possibly to a lesser degree than the resultant from dexamethasone. In addition, FdUrd treatment caused elevation of the DNA 2-bromo-5'deoxyuridine labeling index above control levels in biliary epithelial cells. Dexamethasone and celecoxib each significantly attenuated the FdUrd-induced elevation of DNA labeling index in biliary epithelium. These findings demonstrate the usefulness of this canine model for studying the mechanisms of drug-induced biliary sclerosis and reinforce the hypothesis that blocking inflammation may retard the progression of injury that eventually leads to fibrosis. This study suggests that clinical testing of celecoxib as a preventive for hepatic arterial-FdUrd induced biliary damage could prove valuable.
Descriptors: digestive system, ingestion and assimilation, pharmacology, veterinary medicine, medical sciences, biliary obstruction, digestive system disease, biliary sclerosis, drug induced, colorectal cancer, neoplastic disease, infusaid model 400 implantable pump, drug delivery device.

Fedorov, V.V., G.G. Beloshapko, A.V. Yushmanova, O.F. Sharifov, and L.V. Rosenshtraukh (2003). **Effects of a new class iii antiarrhythmic drug nibentan in a canine model of spontaneous atrial fibrillation.** *European Heart Journal* 24(Abstract Supplement): 391. ISSN: 0195-668X.

Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial premature depolarization, heart disease, prevention and control, reentrant arrhythmia, heart disease, prevention and control, spontaneous atrial fibrillation, heart disease, drug therapy, atrial electrical stimulation, clinical techniques, ik potassium current, atrial effective refractory period, basic cycle length, conduction velocity.

Fleischer, S., M. Sharkey, K. Mealey, E.A. Ostrander, and M. Martinez (2008). **Pharmacogenetic and metabolic differences between dog breeds: their impact on canine medicine and the use of the dog as a preclinical animal model.** *AAPS Journal* 10(1): 110-9.
Abstract: There is limited information describing species related pharmacogenetic differences in animals. Despite the lack of genetic information in veterinary medicine, breed specific responses to endogenous and exogenous substances have been reported across many species. This finding underscores the importance of obtaining insight into the genotypic and phenotypic variation present across breeds. This article provides a summary of the literature pertaining to canine breed differences in physiology, drug response, drug pharmacokinetics, and metabolic idiosyncrasies. The existing knowledge of pedigrees and the known phenotypes and genotypes of dogs provides important information for determining mode of inheritance, penetration, and other major characteristics of heritable traits. Understanding these breed differences will improve canine population predictions (for canine drug products) and may be of value when extrapolating toxicology data from dogs to humans.
Descriptors: dogs genetics, models, animal, pharmaceutical preparations metabolism, pharmacogenetics methods, veterinary medicine methods, drug evaluation, preclinical methods, species specificity.

Forrest, M.J., D. Bloomfield, R.J. Briscoe, P.N. Brown, A.M. Cumiskey, J. Ehrhart, J.C. Hershey, W.J. Keller, X. Ma, H.E. McPherson, E. Messina, L.B. Peterson, W. Sharif Rodriguez, P.K. Siegl, P.J. Sinclair, C.P. Sparrow, A.S. Stevenson, S.Y. Sun, C. Tsai, H. Vargas, M.3. Walker, S.H. West, V. White, and R.F. Woltmann (2008). **Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone.** *British Journal of Pharmacology* 154(7): 1465-73. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: BACKGROUND AND PURPOSE: Inhibition of cholesteryl ester transfer protein (CETP) with torcetrapib in humans increases plasma high density lipoprotein (HDL) cholesterol levels but is associated with increased blood pressure. In a phase 3 clinical study, evaluating the effects of torcetrapib in atherosclerosis, there was an excess of deaths and adverse cardiovascular events in patients taking torcetrapib. The studies reported herein sought to evaluate off-target effects of torcetrapib. EXPERIMENTAL APPROACH: Cardiovascular effects of the CETP inhibitors torcetrapib and anacetrapib were evaluated in animal models. KEY RESULTS: Torcetrapib evoked an acute increase in blood pressure in all species evaluated whereas no increase was observed with anacetrapib. The pressor effect of torcetrapib was not diminished in the presence of adrenoceptor, angiotensin II or endothelin receptor antagonists. Torcetrapib did not have a contractile effect on vascular smooth muscle suggesting its effects in vivo are via the release of a secondary mediator. Treatment with torcetrapib was associated with an increase in plasma levels of aldosterone and corticosterone and, in vitro, was shown to release aldosterone from adrenocortical cells. Increased adrenal

steroid levels were not observed with anacetrapib. Inhibition of adrenal steroid synthesis did not inhibit the pressor response to torcetrapib whereas adrenalectomy prevented the ability of torcetrapib to increase blood pressure in rats. CONCLUSIONS AND IMPLICATIONS: Torcetrapib evoked an acute increase in blood pressure and an acute increase in plasma adrenal steroids. The acute pressor response to torcetrapib was not mediated by adrenal steroids but was dependent on intact adrenal glands.
Descriptors: blood pressure drug effects, cholesterol ester transfer proteins antagonists and inhibitors, oxazolidinones toxicity, quinolines toxicity, adrenal cortex cytology, adrenal cortex drug effects, aldosterone blood, anticholesteremic agents toxicity, corticosterone blood, dogs, drug evaluation, preclinical, macaca mulatta, mice, mice, inbred c57bl, models, animal, muscle, smooth, vascular drug effects, muscle, smooth, vascular metabolism, rats, rats, sprague dawley, species specificity.
Notes: Comments: Comment In: Br J Pharmacol. 2008 Aug;154(7):1379-81.

Francis, R.C., M.S. Reyle Hahn, C. Hohne, A. Klein, I. Theruvath, B. Donaubauer, T. Busch, and W. Boemke (2008). **The haemodynamic and catecholamine response to xenon/remifentanil anaesthesia in Beagle dogs.** *Laboratory Animals* 42(3): 338-49. ISSN: 0023-6772.
NAL Call Number: QL55.A1L3
Abstract: The noble gas xenon seems to have minimal cardiovascular side-effects and so may be an ideal anaesthetic agent when investigating cardiovascular physiology. In comparison with standard modern anaesthetics, we investigated the haemodynamic and hormonal effects of xenon in Beagle dogs. After a 30 min baseline period, anaesthesia was induced with propofol and maintained with either (1) 1.2% isoflurane/70% nitrous oxide (N(2)O), (2) 0.8% isoflurane/0.5 microg/kg/min remifentanil or (3) 63% xenon/0.5 microg/kg/min remifentanil (n = 6 per group). Haemodynamics were recorded and blood samples taken before and 60 min after induction. Mean arterial blood pressure (MAP) was higher in conscious dogs than during isoflurane/N(2)O (86 +/- 2 vs. 65 +/- 2 mmHg, mean +/- SEM) and isoflurane/remifentanil anaesthesia (95 +/- 2 vs. 67 +/- 3 mmHg), whereas MAP did not decrease significantly in response to xenon/remifentanil anaesthesia (96 +/- 4 vs. 85 +/- 6 mmHg). Bradycardia was present during isoflurane/remifentanil (54 +/- 2/min) and xenon/remifentanil (40 +/- 3/min), but not during isoflurane/N(2)O anaesthesia (98 +/- 3/min, $P < 0.05$). Xenon/remifentanil anaesthesia induced the highest reduction in cardiac output (CO) (-61%), and the highest increase in systemic vascular resistance (+120%) among all treatment groups ($P < 0.05$). A simultaneous increase in endogenous adrenaline and noradrenaline concentrations could only be observed in the xenon/remifentanil group, whereas angiotensin II and vasopressin concentrations increased in all groups. In conclusion, xenon/remifentanil anaesthesia maintains MAP but reduces heart rate and CO and is associated with a considerable stimulation of vasopressor hormones in Beagle dogs. Therefore, xenon/remifentanil exerts a new quality of adverse haemodynamic effects different from volatile anaesthetics and may not perform better during studies of cardiovascular physiology.
Descriptors: anesthetics, inhalation pharmacology, cardiovascular system drug effects, catecholamines blood, dogs physiology, models, animal, piperidines pharmacology, xenon pharmacology, aldosterone blood, atrial natriuretic factor blood, dogs blood, endothelin 1 blood, hemodynamics drug effects, isoflurane pharmacology, nitrous oxide pharmacology, random allocation, renin blood.

Freitas, C.F., R. Faro, D. Dragosavac, M. Clozel, G. De Nucci, and E. Antunes (2004). **Role of endothelin-1 and thromboxane a2 in the pulmonary hypertension induced by heparin-protamine interaction in anesthetized dogs.** *Journal of Cardiovascular Pharmacology* 43(1): 106-112. ISSN: 0160-2446.

Abstract: This study aimed to study the role of thromboxane A2 (TXA2) and endothelin-1 (ET-1) in the pulmonary hypertension induced by interaction of heparin-protamine in anesthetized dogs. The effect of inhaled nitric oxide (NO) was also investigated in this model. Dogs were anesthetized and instrumented for acquisition of mean arterial blood pressure, mean arterial pulmonary pressure (MPAP), and pulmonary pressure gradient (PPG). Cardiac index (CI), heart rate, and index of systemic vascular resistance were also obtained. Intravenous administration of heparin (500 IU/kg) 3 minutes before protamine (10 mg/kg) caused marked pulmonary hypertension, as evaluated by the increase in MPAP and PPG. This was accompanied by systemic hypotension, CI decrease, and tachycardia. Indomethacin (10 mg/kg), dazoxiben (10 mg/kg), or tezosentan (10-mg/kg bolus plus 10-mg/kg/h infusion) significantly reduced the increase in MPAP and PPG, but had no effect on the systemic hypotension. Similar results were obtained with inhaled NO (3 ppm). Plasma TXB2 levels were markedly elevated during the pulmonary hypertension, and this was abolished in indomethacin-treated dogs. Our study shows that interaction of heparin-protamine in anesthetized dogs lead to TXA2- and ET-1-mediated pulmonary hypertension. Drugs that interfere with the synthesis of these mediators as well as inhaled NO may be of beneficial value to control this disorder.

Descriptors: cardiovascular system, transport and circulation, pharmacology, pulmonary hypertension, vascular disease, tachycardia, heart disease, cardiac index, heart rate, heparin protamine interaction, mean arterial blood pressure, mean arterial pulmonary pressure, pulmonary pressure gradient, systemic vascular resistance index.

Fryer, R.M., L. Preusser, S. Calzadilla, Y. Hu, H. Xu, K. Marsh, B. Cox, C.T. Lin, M. Gopalakrishnan, and G. Reinhart (2004). **A-278637, a novel atp-sensitive potassium channel opener: hemodynamic comparison to zd-6169, way-133537 and nifedipine in the anesthetized canine**. *FASEB Journal* 18(4-5): Abst. 404.3. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: cardiovascular system, transport and circulation, pharmacology, urinary system, chemical coordination and homeostasis, overactive bladder, urinary incontinence, urologic disease, therapy .

Gamez, R., R. Mas, M. Noa, R. Menendez, H. Garcia, J. Gonzalez, Y. Perez, and E. Goicochea (2004). **Effects of chronic administration of d-003, a mixture of sugar cane wax high molecular acids, in beagle dogs**. *Drugs Under Experimental and Clinical Research* 30(2): 75-88. ISSN: 0378-6501.

Abstract: D-003 is a mixture of high molecular weight aliphatic primary acids purified from sugar cane wax (Saccharum officinarum, Q with cholesterol-lowering and antiplatelet effects. Previous studies, including a 6-month study conducted in rats, have shown no D-003-related toxicity. The present study was undertaken to investigate the effects of D-003 orally administered for 9 months in beagle dogs. The animals were randomly distributed in three groups: a control group receiving the vehicle only and two groups orally adminis-

tered D-003 (200 and 400 mg/kg). Body weight gain, food consumption and clinical signs were controlled throughout the study. The effects of D-003 on collagen-induced platelet aggregation, bleeding time (B T) and coagulation parameters (prothrombin time and kaolin-activated thromboplastin time) were also investigated. Most blood biochemistry and hematological parameters were assessed at baseline and after 6 and 9 months of treatment, while total cholesterol (TC), triglycerides, platelet aggregation, B T and coagulation parameters were determined at baseline and after 9 months of treatment. At study completion, the animals were sacrificed. D-003 at a dose of 200 and 400 mg/kg significantly reduced TC ($p < 0.05$), significantly inhibited platelet aggregation and increased BT compared with levels in controls. Data analyses of body weight gain, food consumption, clinical observations, the remaining blood biochemistry and hematology indicators (including coagulation parameters, organ weight ratios and histopathological findings) showed no trends with D-003 doses or significant differences between control animals and treated groups. In conclusion, D-003 administered for 9 months to beagle dogs induced the expected effects with no evidence of drug-related toxicity.
Descriptors: clinical chemistry, allied medical sciences, pharmacology, toxicology .

Genissel, P., Y. Chodjania, J.L. Demolis, I. Ragueneau, and P. Jaillon (2004). **Assessment of the sustained release properties of a new oral formulation of trimetazidine in pigs and dogs and confirmation in healthy human volunteers**. *European Journal of Drug Metabolism and Pharmacokinetics* 29(1): 61-68. ISSN: 0378-7966.
Abstract: The pharmacokinetics of immediate (IR) and modified release (MR) trimetazidine (TMZ) in dogs and pigs, have been compared under single dose conditions, then predicted at steady-state under conditions mimicking an actual human pharmacokinetic study. In both animal species, the MR tablet has demonstrated sustained release properties, as assessed by delayed time to peak and increased mean absorption times. Multiple dose simulations in dogs revealed a delayed time to peak (3.0 vs. 1.0 h), a decrease in peak plasma concentration (544 vs. 659 mug/L), an increase in trough concentrations (115 vs. 63 mug/L), a decrease in peak-trough fluctuation (141 vs. 193%), and an increase in plateau time (5.5 vs. 4.9 h). Qualitatively similar changes were simulated in pigs. These properties have then been verified in humans where a TMZ MR 35 mg b.i.d regimen did provide similar total exposure, increased plateau time (11 vs. 4 h), decreased peak-trough fluctuation (86 vs. 121%), a 31% increase in trough concentrations, and no increase in inter-individual variability as compared to a TMZ IR 20 mg t.i.d. regimen. Furthermore, the TMZ MR 35 mg b.i.d. regimen is likely to result in improved patient compliance and better patient anti-ischemic protection in the early morning.
Descriptors: metabolism, pharmacology, drug metabolism.

Georges, G.E., R. Storb, J.M. Zaucha, A.G. Taranova, T. Gooley, and R.A. Nash (2003). **Il-2 does not enhance the conversion to complete donor chimerism following nonmyeloablative hematopoietic cell transplantation in dogs.** *Bone Marrow Transplantation* 31(11): 1027-1031. ISSN: 0268-3369.
Abstract: A dog model of stable mixed hematopoietic chimerism was established in which leukocyte-antigen-identical littermates receive nonmyeloablative total body irradiation before hematopoietic cell transplantation and postgrafting immunosuppression with mycopheno-

late mofetil and cyclosporine. Unmodified donor lymphocyte infusion (DLI) into stable mixed chimeras failed to increase donor chimerism, while DLI from donors sensitized to recipient minor-histocompatibility antigens promptly converted all recipients to complete donor chimerism. This established a model for studying approaches to enhance the graft-versus-host (GVH)-effect, a potential surrogate for graft-versus-leukemia activity. We asked if interleukin-2 (IL-2) given after unmodified DLI could result in reliable conversion to complete donor chimerism. IL-2, 4X105 IU/kg/day, was administered to six mixed chimeric dogs for 14 days. Four dogs received unmodified DLI with IL-2. At 20-40 weeks after DLI, all dogs remained mixed chimeras. For the two recipients of IL-2 only, mixed chimerism also remained unchanged. These results show that IL-2 given with DLI after nonmyeloablative transplantation in dogs is not effective in reliably converting mixed to complete donor chimerism.

Descriptors: immune system, chemical coordination and homeostasis, pharmacology, nonmyeloablative hematopoietic cell transplantation, clinical techniques, therapeutic and prophylactic techniques, total body irradiation, laboratory techniques, unmodified donor lymphocyte infusion, complete donor chimerism, graft vs host effect, immunosuppression, mixed donor chimerism.

Guo Zhi Bin , Li Qing , Cao Hong Yu , and Xu Zhi (2003). **Comparative study of propafenone and procainamide on canine ischemic ventricular tachyarrhythmias.** *Zhongguo Yaolixue Yu Dulixue Zazhi* 17(5): 360-365. ISSN: 1000-3002.

Abstract: AIM: To observe the electrophysiologic effects of propafenone (Prop) on canine ischemic ventricular tachyarrhythmias and compared with those of procainamide (PA), so as to evaluate the effect and mechanism of Prop on ischemic ventricular tachyarrhythmias. METHODS: A canine ischemic ventricular tachyarrhythmia model was established by the left anterior descending coronary artery occlusion for 2 h and reperfusion. Five to eight days later, open-chest dogs were given programmed electrical stimulation (PES), and electrophysiologic data were measured by electrocardiogram (ECG). RESULTS: Both Prop and PA distinctly lengthened the QTc interval ($P<0.01$) and effective refractory period (ERP) of normal and ischemic ventricular myocardium respectively ($P<0.01$), decreased the dispersion of ERP in ischemic myocardium and in left ventricle ($P<0.01$), and increased the diastolic excitability threshold of normal and ischemic ventricular myocardium remarkably ($P<0.01$). Prop and PA effectively prevented PES- or ischemia-induced ventricular tachycardia or ventricular fibrillation ($P<0.05$, or $P<0.01$). CONCLUSION: The canine model is a worthy and reliable one. Prop and PA may be effective in preventing the onset of ventricular tachycardia or ventricular fibrillation after myocardial ischemic damage. The antiarrhythmic effects of both drugs are similar.

Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemic ventricular tachyarrhythmia, heart disease, myocardial infarction, heart disease, vascular disease, ventricular fibrillation, ventricular tachycardia, electrocardiography, clinical techniques, diagnostic techniques, programmed electrical stimulation, experimental surgical techniques, laboratory techniques, qtc interval, comparative study, diastolic excitability threshold, disease onset, disease prevention, effective refractory period, electrophysiologic data.

Halpenny, M., F. Markos, H.M. Snow, P.F. Duggan, E. Gaffney, D.P. O'Connell, and G.D. Shorten (2001). **Effects of prophylactic fenoldopam infusion on renal blood flow and renal tubular function during acute hypovolemia in anesthetized dogs.** *Critical Care Medicine.* 29(4): 855-860. ISSN: 0090-3493.

Abstract: OBJECTIVE: It was hypothesized that fenoldopam mesylate, a selective dopamine agonist, may preserve renal perfusion and decrease tubular oxygen consumption during states of hypoperfusion, such as hypovolemic shock. The objective of this study was to quantify the effects of fenoldopam (0.1 microg x kg(-1) x min(-1)) on renal blood flow, urine output, creatinine clearance, and sodium clearance in pentobarbital anesthetized dogs that had undergone partial exsanguination to acutely decrease cardiac output. DESIGN: Prospective, randomized, controlled experiment. SETTING: University-based animal laboratory and research unit. SUBJECTS: Eight female beagle dogs. INTERVENTIONS: Arterial blood pressure, heart rate, cardiac output, renal blood flow, urine output, creatinine clearance, and fractional excretion of sodium were measured and calculated at four times: a) before infusion of fenoldopam or normal saline; b) during infusion of fenoldopam or normal saline (1 hr); c) during a 90-min period of hypovolemia (induced by acute partial exsanguination), with concurrent infusion of fenoldopam or normal saline; and d) during a 1-hr period after retransfusing the dogs. MEASUREMENTS AND MAIN RESULTS: Administration of fenoldopam (0.1 microg x kg(-1) x min(-1)) was not associated with hemodynamic instability. Renal blood flow and urine output decreased significantly from baseline (p <.01) during the hypovolemic period in the placebo group (72 +/- 20 to 47 +/- 6 mL/min and 0.26 +/- 0.15 to 0.08 +/- 0.05 mL/min, respectively) but not in the fenoldopam group (75 +/- 14 to 73 +/- 17 mL/min and 0.3 +/- 0.19 to 0.14 +/- 0.05 mL/min, respectively). Creatinine clearance and fractional excretion of sodium decreased significantly from baseline (p <.01) in the placebo group during the hypovolemic period (3.0 +/- 0.4 to 1.8 +/- 0.8 mL x kg(-1) x min(-1) and 1.7% +/- 0.9% to 0.4% +/- 0.2%, respectively) but not in the dogs that received fenoldopam (3.0 +/- 1.0 to 2.9 +/- 0.5 mL x kg(-1) x min(-1) and 1.9% +/- 1.1% to 1.7% +/- 2.7%, respectively). CONCLUSIONS: Fenoldopam ablated the tubular prerenal response to profound hypovolemia and maintained renal blood flow, glomerular filtration rate, and natriuresis without causing hypotension. This suggests that fenoldopam may have a renoprotective effect in acute ischemic injury.

Descriptors: animal model, female, beagle dogs, hypovolemia, fenoldopam, blood flow, glomerular filtration rate, natriuresis.

Han, J., J.C. Kim, M.K. Chung, B. Kim, and D.R. Choi (2003). **Subacute toxicity and toxicokinetics of a new antibiotic, dw-224a, after single and 4-week repeated oral administration in dogs.** *Biological and Pharmaceutical Bulletin* 26(6): 832-839. ISSN: 0918-6158.

NAL Call Number: QP501

Abstract: The subacute toxicity and toxicokinetics of a new fluoroquinolone antibiotic, DW-224a, were evaluated after single (on the 1st day) and 4-week (on the 28th day) oral administration of the drug at doses of 0 (to serve as a control), 10, 30, and 90 mg/kg/d, to male and female dogs (n = 3 for male and female dogs for each dose). During the test period, clinical signs, mortality, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, organ weight and histopathology were examined. The 4-week repeated oral dose of DW-224a resulted in vomiting, salivation, increased serum

cholesterol level, and atrophy of thymus and testes. The target organ was determined to be the thymus and testes. The absolute toxic dose of DW-224a was 30 mg/kg and the level at which no adverse effects were observed was 10 mg/kg for both sexes. There were no significant gender differences in the pharmacokinetic parameters of DW-224a for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of DW-224a were dose independent after a single oral administration; the time to reach the peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentration-time curve from time zero to 24 h in plasma (AUC0-24 h) were not significantly different among the three doses. The accumulation of DW-224a after 4-week oral administration was not notable at the toxic dose of 90 mg/kg/d. For example, after 4-week administration, the dose-normalized AUC0-24 h value at 90 mg/kg/d (7.69, 7.05 mug h/ml) was not significantly greater than that at 10 mg/kg/d. After 4-week oral administration, the dose-normalized Cmax and AUC0-24 h at 90 mg/kg/d were not significantly higher and greater, respectively, than those after a single oral administration.
Descriptors: pharmacology, veterinary medicine, medical sciences, ophthalmoscopy, clinical techniques, therapeutic and prophylactic techniques, urinalysis, laboratory techniques.

Han, J., H.C. Shin, J.C. Kim, and B. Kim (2004). **Subacute toxicity and toxicokinetics of cj-10882, a type iv phosphodiesterase inhibitor, after 4-week repeated oral administration in dogs.** *Food and Chemical Toxicology* 42(3): 373-380. ISSN: 0278-6915.
NAL Call Number: 391.8 F73
Abstract: The subacute toxicity and toxicokinetics of a type IV phosphodiesterase inhibitor, CJ-10882, were evaluated after single (on the 1st day) and 4-week (on the 27th day) oral administration of the drug, in doses of 0 (to serve as a control), 2, 10 and 50 mg/kg/day, to male and female dogs (n=3 for male and female dogs for each dose). During the test period, clinical signs, mortality, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, organ weight and histopathology were examined. The 4-week repeated oral doses of CJ-10882 resulted in salivation, vomiting, and atrophy of the thymus. The absolute toxic dose was 50 mg/kg/day and the level at which no adverse effects were observed was 2 mg/kg/day for male and female dogs. There were no significant gender differences in the pharmacokinetic parameters of CJ-10882 for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of CJ-10882 were dose independent after a single oral administration; the time to reach a peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentration-time curve from time zero to 8 h in plasma (AUC0-8 h) were not significantly different among three doses. The accumulation of CJ-10882 after 4-week oral administration was not notable at the toxic dose of 50 mg/kg/day. For example, after 4-week administration, the dose-normalized AUC0-8 h value at 50 mg/kg/day (0.132 mug h/ml) was not significantly greater than that at 10 mg/kg/day (0.131 mug h/ml). After 4-week oral administration, the dose-normalized Cmax and AUC0-8 h at 50 mg/kg/day were not significantly higher and greater, respectively, than those after the single oral administration.
Descriptors: pharmacology, toxicology, salivation, vomiting.

Harris, S.R., J.I. Gedge, A.N.R. Nedderman, S.T. Roffey, and M. Savage (2004). **A sensitive hplc-ms-ms assay for quantitative determination of midazolam in dog plasma**. *Journal of Pharmaceutical and Biomedical Analysis* 35(1): 127-134. ISSN: 0731-7085.
NAL Call Number: RS400
Descriptors: methods and techniques, pharmacology, 96 well oasis mcx solid phase extraction plates, laboratory equipment, hplc ms ms assay, high performance liquid chromatography dual mass spectrometry assay, chromatographic techniques, laboratory techniques, spectrum analysis techniques, accuracy, clinical pharmacokinetics, drug interactions, inter assay precision, intra assay precision, pharmacokinetic parameters, specificity .

Hashimoto, N., I. Takeyoshi, H. Tsutsumi, Y. Sunose, M. Tokumine, O. Totsuka, S. Ohwada, K. Matsumoto, and Y. Morishita (2004). **Effects of a bradykinin b2 receptor antagonist on ischemia-reperfusion injury in a canine lung transplantation model**. *Journal of Heart and Lung Transplantation* 23(5): 606-613. ISSN: 1053-2498.
Abstract: Background: This study investigated the effects of a bradykinin B, receptor antagonist, FR173657 (FR), on ischemia-reperfusion (I/R) injury in a canine lung transplantation model. Methods: Eighteen pairs of weight-matched dogs were randomly divided into 3 groups. Six pairs were assigned to the FR(D+R) group, in which FR (100 nmol/kg/h) was administered to the transplant donor continuously beginning 30 minutes before ischemia until the onset of ischemia, and FR was administered to the transplant recipient beginning 30 minutes before reperfusion and continuing for 2 hours after reperfusion. Another 6 pairs of dogs were assigned to the FR(R) group, in which FR was administered only to the recipient in the same manner as in the FR(D + R) group. The other pairs were assigned to the control group, in which vehicle alone was administered. Orthotopic left lung transplantation was performed after 12-hour cold storage in Euro-Collins solution. Fifteen minutes after reperfusion, the right pulmonary artery and the right stem bronchus were ligated. The animals were measured for 4 hours after reperfusion for left pulmonary vascular resistance (L-PVR), cardiac output (CO), arterial oxygen pressure (Pao2) and alveolar-arterial oxygen pressure difference (A-aDo2). Lung specimens were harvested for measurement of the wet-to-dry lung weight ratio (WDR), histopathologic studies and polymorphonuclear neutrophil (PMN) count. Results: Compared with the control group, Pao2, A-aDo2, L-PVR and CO were all significantly ($p < 0.05$) improved and WDR significantly ($p < 0.05$) lower in both the FR(D+R) and FR(R) groups. Moreover, in the FR-treatcd groups, histologic tissue edema was mild, and PMN infiltration was significantly ($p < 0.05$) reduced. Conclusions: The bradykinin B, receptor antagonist, FR173657, ameliorates I/R injury in lung grafts, indicating that protection of lung grafts can be achieved by the administration of FR solely to the transplant.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, ischemia reperfusion injury, injury, vascular disease, pathology, histopathologic study, histology and cytology techniques, laboratory techniques, lung transplantation, clinical techniques, therapeutic and prophylactic techniques, orthotopic left lung transplantation, alveolar arterial oxygen pressure difference, arterial oxygen pressure, cardiac output, left pulmonary vascular resistance, wet to dry lung weight ratio.

Hatada, K., L.M. Riou, M. Ruiz, R.L. Lima, A.R. Goode, D.D. Watson, G.A. Beller, and D.K. Glover (2003). **Comparison between the myocardial uptake of 99mtcn-dbodc5 and 201ti during vasodilator stress in a canine model of a critical coronary stenosis.** *Journal of the American College of Cardiology* 41(6 Supplement A): 443A. ISSN: 0735-1097.
NAL Call Number: RC681.A1
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, coronary stenosis, heart disease, vascular disease, myocardial blood flow, vasodilator stress

Haushalter, T.M., G.S. Friedrichs, D.L. Reynolds, M. Barecki Roach, G. Pastino, R. Hayes, and A.S. Bass (2008). **The cardiovascular and pharmacokinetic profile of dofetilide in conscious telemetered beagle dogs and cynomolgus monkeys.** *British Journal of Pharmacology* 154(7): 1457-64. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: BACKGROUND AND PURPOSE: The effects of dofetilide were studied in monkeys and dogs. Pharmacokinetic data were generated together with the monitoring of cardiovascular changes in order to compare effects relative to human exposure. EXPERIMENTAL APPROACH: Beagle dogs and cynomolgus monkeys were telemetered to collect arterial blood pressure, heart rate and ECG for 6 h after selected oral doses of dofetilide. Pharmacokinetic parameters were determined for each dose. KEY RESULTS: Dogs: increases in the QT(c) interval reached 56 ms in dogs dosed with 0.3 mg kg(-1) of dofetilide. Premature ventricular contractions and right bundle branch block were evident at this dose, without changes in cardiovascular parameters. The mean C(max) values were 3.35 and 60.15 ng mL(-1) at doses of 0.03 and 0.3 mg kg(-1), respectively. Monkeys: increases in QT(c) intervals reached 40-50 ms after 0.03 mg kg(-1). T-wave changes were observed after 0.03 mg kg(-1) without changes in cardiovascular parameters. The mean C(max) values following oral doses of 0.01 and 0.03 mg kg(-1) were 0.919 ng mL(-1) and 1.85 ng mL(-1), respectively. CONCLUSIONS AND IMPLICATIONS: Despite dofetilide exposure comparable to that in humans, QT(c) responses in dogs were greater than those reported in humans. A comparable human dose used in the monkey achieved only half of the exposure but was associated with twofold greater increases in QT(c). Our data support the view that safety risk assessments of new drugs in animal models should ensure that the clinical therapeutic range of exposure is achieved and any untoward effects interpreted accordingly.
Descriptors: anti arrhythmia agents toxicity, long qt syndrome chemically induced, models, animal, phenethylamines toxicity, sulfonamides toxicity, administration, oral, anti arrhythmia agents administration and dosage, anti arrhythmia agents pharmacokinetics, blood pressure drug effects, dogs, dose response relationship, drug, electrocardiography, heart rate drug effects, macaca fascicularis, phenethylamines administration and dosage, phenethylamines pharmacokinetics, species specificity, sulfonamides administration and dosage, sulfonamides pharmacokinetics, telemetry.

Hayashi, K. (2003). **Effects of angiotensin ii receptor antagonist on intestinal mucosal oxygenation during canine isovolemic hemodilution with hydroxyethyl starch.** *Japanese Journal of Anesthesiology* 52(6): 603-610. ISSN: 0021-4892.
Abstract: Background: Although isovolemic hemodilution can be used clinically to reduce the need for blood transfusion, the critical hemoglobin level and severe indequacy of tissue

oxygenation induced by hemodilution remain unknown. Methods: Anesthetized dogs were submitted to graded hemodilution (20% and 40% blood volume reductions of estimated circulating blood volume) replaced with 10% hydroxyethyl starch. The effect of angiotensin II receptor (AT-II) antagonist, candesartan, on the intestinal mucosal oxygenation was assessed by tonometric method. Results: The splanchnic blood flow, measured by transit-time flow meters, and intestinal mucosal oxygenation were maintained well during 20% blood volume reduction without AT-II antagonist. By severe blood volume reduction, however, inadequate oxygenation was observed without, but not with AT-II antagonist. Conclusions: These results suggest the protective effect of AT-II antagonist on intestinal perfusion during severe isovolemic hemodilution. Further investigation will be needed in patients undergoing major surgery with large anticipated blood loss.
Descriptors: blood and lymphatics, transport and circulation, pharmacology, isovolemic hemodilution, clinical techniques, therapeutic and prophylactic techniques.
Language of Text: Japanese.

Hirata, T., T. Funatsu, Y. Keto, M. Nakata, and M. Sasamata (2007). **Pharmacological profile of ramosetron, a novel therapeutic agent for IBS.** *Inflammopharmacology* 15(1): 5-9. ISSN: 0925-4692.
Abstract: Ramosetron is a potent and selective serotonin (5-HT)(3) receptor antagonist that has been shown to affect abnormal colonic function and abdominal pain in animals. Ramosetron (0.3 to 100 microg/kg, p.o.) has been found to significantly suppress abnormal defecation induced by conditioned-fear stress (CFS), restraint stress, corticotropin releasing factor (CRF) and 5-HT in rats and mice, and these effects were more potent than those of alosetron, cilansetron or loperamide. On the other hand, ramosetron (3,000 microg/kg, p. o., once daily for 7 days) did not inhibit normal defecation in dogs while tiquizium significantly inhibited it. Ramosetron (3 to 100 microg/kg, p. o.) also significantly prevented CFS-induced acceleration of colonic transit and CRF-induced abnormal water transport in rats, respectively. Moreover, ramosetron (0.3 to 3 microg/kg, p. o.) significantly suppressed restraint stress-induced decrease in colonic pain threshold, an effect not observed with loperamide. These results indicate that ramosetron produce beneficial clinical effects on IBS symptoms.
Descriptors: benzimidazoles pharmacology, irritable bowel syndrome drug therapy, serotonin antagonists pharmacology, abdominal pain drug therapy, benzimidazoles therapeutic use, defecation drug effects, diarrhea drug therapy, dogs, gastrointestinal transit drug effects, mice, models, animal, rats, serotonin antagonists therapeutic use.

Hirota, K., Y. Hashimoto, T. Sato, H. Yoshioka, T. Kudo, A. Matsuki, and D.G. Lambert (2001). **Bronchoconstrictive and relaxant effects of lidocaine on the airway in dogs.** *Critical Care Medicine.* 29(5): 1040-4. ISSN: 0090-3493.
Abstract: OBJECTIVE: Intravenous lidocaine commonly is used to treat ventricular arrhythmias and to attenuate reflex airway constriction and intracranial pressure elevation during airway manipulation in intensive care units. There is much controversy as to the actions of lidocaine on the airway, so the aim of this study was to compare, in detail, the actions of lidocaine with those of bupivacaine and procaine on airway caliber and the associated changes in plasma catecholamine concentrations in the dog. DESIGN: Prospective, randomized,

controlled experimental in vivo and in vitro study. SETTING: A university research laboratory. SUBJECTS: Mongrel dogs. INTERVENTIONS: In the first experiment, we evaluated the effects of intravenous local anesthetics--lidocaine 0-10 mg/kg (n = 7), bupivacaine 0-2.5 mg/kg (n = 7), or procaine 0-20 mg/kg (n = 7)--on basal airway tone. In second experiment, histamine (10 microg/kg + 500 microg x kg(-1) x hr(-1), n = 6), serotonin (10 microg/kg + 500 microg x kg(-1) x hr(-1), n = 7), and methacholine (0.5 microg/kg + 300 microg x kg(-1) x hr(-1), n = 7) were infused to determine the effects of lidocaine (0-10 mg/kg) on agonist-induced bronchoconstriction. In addition, the actions of lidocaine on vagal nerve stimulation were examined (n = 7). MEASUREMENTS AND MAIN RESULTS: Bronchial cross-sectional area at the third bronchial bifurcation of dogs was monitored continuously through a fiberoptic bronchoscope. In the first experiment, all local anesthetics produced a dose-dependent decrease in basal bronchial cross-sectional area. In the second experiment, lidocaine significantly potentiated histamine and serotonin-induced bronchoconstriction. In contrast, lidocaine antagonized methacholine- and vagal nerve stimulation-induced bronchoconstriction. CONCLUSION: We have clearly demonstrated that lidocaine may produce direct bronchoconstriction and worsen some agonist-induced bronchoconstriction, but it prevents reflex airway constriction. Therefore, we suggest that this agent be used with caution in asthmatics.

Descriptors: animal model, mongrel dogs, intravenous lidocaine, ventricular arrhythmias, reflex airway constriction, intracranial pressure elevation.

Holm, R., C.J.H. Porter, G.A. Edwards, A. Mullertz, H.G. Kristensen, and W.N. Charman (2003). **Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (smedds) containing structured triglycerides.** *European Journal of Pharmaceutical Sciences* 20(1): 91-97. ISSN: 0928-0987.

NAL Call Number: 396.8 P4933

Abstract: The potential for lipidic self-microemulsifying drug delivery systems (SMEDDS) containing triglycerides with a defined structure, where the different fatty acids on the glycerol backbone exhibit different metabolic fate, to improve the lymphatic transport and the portal absorption of a poorly water-soluble drug, halofantrine, were investigated in fasted lymph cannulated canines. Two different structured triglycerides were incorporated into the SMEDDS; 1,3-dioctanoyl-2-linoleyl-sn-glycerol (C8:0-C18:2-CS:0) (MLM) and 1,3-dilinoyl-2-octanoyl-sn-glycerol (C18:2-C8:0-C18:2) (LML). A previously optimised SMEDDS formulation for halofantrine, comprising of triglyceride, Cremophor EL, Maisine 35-1 and ethanol was selected for bioavailability assessment. The extent of lymphatic transport via the thoracic duct was 17.9% of the dose for the animals dosed with the MLM SMEDDS and 27.4% for LML. Also the plasma availability was affected by the triglyceride incorporated into the multi-component delivery system and availabilities of 56.9% (MLM) and 37.2% (LML) were found. These data indicate that the pharmaceutical scientist can use the structure of the lipid to affect the relative contribution of the two absorption pathways. The MLM formulation produced a total bioavailability of 74.9%, which is higher than the total absorption previously observed after post-prandial administration. This could indicate the utility of disperse lipid-base formulations based on structured triglycerides for the oral delivery of halofantrine, and potentially other lipophilic drugs.

Descriptors: equipment apparatus devices and instrumentation, pharmacology, cannulation, clinical techniques, self microemulsifying drug delivery systems, smedds, drug delivery device.

Horais, K., V. Hruby, S. Rossi, D. Cizkova, C. Meschter, R. Dorr, and T.L. Yaksh (2003). **Effects of chronic intrathecal infusion of a variant delta opioid agonist in dogs.** *Toxicological Sciences* 71(2): 263-275. ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Abstract: To define the effects of chronic spinal exposure to a highly selective variant delta opioid agonist c(DPen2,DPen5)enkephalin (DPDPE), adult beagles were prepared with chronic lumbar intrathecal catheters. Groups of dogs received intrathecal infusions (100 mul/h) of saline (vehicle), DPDPE 3 mg/ml or 6 mg/ml for 28 days. Over the 28-day period, saline or 3 mg/ml showed minimal changes in neurological function, whereas in the 6 mg/ml animals, prominent hind limb dysfunction evolved over the 28-day interval. Histopathology in control animals displayed a modest pericatheter reaction considered normal for this model. Dogs receiving DPDPE (three of four at 6 mg/ml and one of four at 3 mg/ml) but not saline (zero of four) developed large inflammatory masses (granulomas) in the intrathecal space located proximal to the catheter tip. In these masses, severe chronic inflammatory changes in combination with necrosis and fibrosis was detected. Occasional focal destruction of neuropil was detected also in the adjacent spinal cord parenchyma. These masses contained extensive accumulation of mouse antihuman macrophages (MAC)-positive inflammatory cells expressing tumor necrosis factor-alpha (TNF-alpha), revealing infiltration of macrophages, granulocytes, and monocytes. In separate animals, prepared with dual intrathecal catheters, lumbar CSF was sampled at specified time points following intrathecal bolus (3 mg/ml) and 24 h DPDPE infusion (3 mg/ml and 6 mg/ml). Steady-state cerebrospinal fluid (CSF) DPDPE levels were 18.6 +- 1.0 and 22.6 +- 4.0 mug/ml for 3 mg/ml and 6 mg/ml infusions respectively. These results indicate that this variant delta opioid agonist DPDPE produces a concentration and time-dependent formation of an intrathecal inflammatory mass.
Descriptors: neural coordination, pharmacology, toxicology, hind limb dysfunction, nervous system disease, toxicity, drug induced, intrathecal granuloma.

Humbert, B., P. Nguyen, L. Martin, H. Dumon, G. Vallette, P. Maugere, and D. Darmaun (2007). **Effect of glutamine on glutathione kinetics in vivo in dogs.** *Journal of Nutritional Biochemistry* 18(1): 10-6. ISSN: 0955-2863.
NAL Call Number: QP141.A1J54
Abstract: To determine whether glutamine affects glutathione (GSH, gamma-glutamyl-cysteinyl-glycine) metabolism, seven healthy beagle dogs received 6-h infusions of [(15)N] glutamate and [(13)C]leucine after a 3-day fast. Isotope infusions were performed during oral feeding with an elemental regimen, supplemented with either l-glutamine or an isonitrogenous amino acid mixture, on two separate days and in randomized order. Timed blood samples were obtained, and a surgical duodenal biopsy was performed after 6 h of isotope infusion. GSH fractional synthesis rate (FSR) was assessed from [(15)N]glutamate incorporation into blood and gut GSH, and duodenal protein synthesis from [(13)C]leucine incorporation into gut protein. Glutamine supplementation failed to alter erythrocyte GSH concentration (2189+/-86 vs. 1994+/-102 micromol L(-1) for glutamine vs. control; ns)

or FSR (64+/-17% vs. 74+/-20% day(-1); ns). In the duodenum, glutamine supplementation was associated with a 92% rise in reduced/oxidized GSH ratio (P=.024) and with a 44% decline in GSH FSR (96+/-15% day(-1) vs. 170+/-18% day(-1); P=.005), whereas total GSH concentration remained unchanged (808+/-154 vs. 740+/-127 micromol kg(-1); P=.779). We conclude that, in dogs receiving enteral nutrition after a 3-day fast: (1) glutamine availability does not affect blood GSH, and, (2) in contrast, in the duodenum, the preserved GSH pool, along with a decreased synthesis rate, suggests that glutamine may maintain GSH pool and intestinal redox status by acutely decreasing GSH utilization.
Descriptors: glutamine pharmacology, glutathione metabolism, dogs, duodenum metabolism, enteral nutrition, erythrocytes chemistry, glutamic acid blood, glutamine blood, glutathione biosynthesis, glutathione blood, intestines metabolism, kinetics, models, animal, oxidation reduction, protein biosynthesis.

Imai, T., T. Nomura, M. Aso, and M. Otagiri (2003). **Enantiospecific disposition of pranoprofen in beagle dogs and rats.** *Chirality* 15(4): 312-317. ISSN: 0899-0042.
Abstract: The pharmacokinetic characteristics of pranoprofen enantiomer were examined and compared with the disposition of the corresponding isomer after the administration of racemic pranoprofen to beagle dogs and rats. The plasma levels of (+)-(S)-isomer were significantly higher than those of (-)-(R)-isomer in dogs and rats by either intravenous or oral administration. Although the oral bioavailability and absorption rate constant between the (-)-(R)- and (+)-(S)-form was the same, the elimination rate constant of the (+)-(S)-form was significantly lower than that of the (-)-(R)-form in both dogs and rats. This discrepancy can be explained on the basis of differences in protein binding and the metabolism of the two enantiomers. The (-)-(R)-isomer was predominantly conjugated depending on its higher free plasma level and its faster metabolic rate than the (+)-(S)-form, and thus was excreted more rapidly in the urine and bile in the form of pranoprofen glucuronide. Furthermore, a (-)-(R)- to (+)-(S)-inversion occurred to the extent of 14% in beagle dogs, but not in rats. This chiral inversion might be an important factor in the slow elimination of the (+)-(S)-form in dogs. The most efficient organ for chiral inversion was the liver, followed by kidney and intestine.
Descriptors: metabolism, pharmacology, acyl glucuronidation, chiral inversion, protein binding.

Imanishi, M., Y. Tomishima, S. Itou, H. Hamashima, Y. Nakajima, K. Washizuka, M. Sakurai, S. Matsui, E. Imamura, K. Ueshima, T. Yamamoto, N. Yamamoto, H. Ishikawa, K. Nakano, N. Unami, K. Hamada, Y. Matsumura, F. Takamura, and K. Hattori (2008). **Discovery of a novel series of biphenyl benzoic acid derivatives as potent and selective human beta3-adrenergic receptor agonists with good oral bioavailability. Part I.** *Journal of Medicinal Chemistry* 51(6): 1925-44. ISSN: 0022-2623.
NAL Call Number: RS402
Abstract: A novel class of biphenyl analogues containing a benzoic acid moiety based on lead compound 8i have been identified as potent and selective human beta 3 adrenergic receptor (beta 3-AR) agonists with good oral bioavailability and long plasma half-life. After further substituent effects were investigated at the terminal phenyl ring of lead compound 8i, we have discovered that more lipophilic substitution at the R position improved potency and selectivity. As a result of these studies, 10a and 10e were identified as the leading candi-

dates with the best balance of potency, selectivity, and pharmacokinetic profiles. In addition, compounds 10a and 10e were evaluated to be efficacious for a carbachol-induced increase of intravesical pressure, such as an overactive bladder model in anesthetized dogs. This represents the first demonstrated result dealing with beta 3-AR agonists.
Descriptors: adrenergic beta agonists pharmacology, benzoic acids pharmacology, biphenyl compounds chemistry, receptors, adrenergic, beta 3 agonists, administration, oral, adrenergic beta agonists chemical synthesis, adrenergic beta agonists chemistry, anesthesia, benzoic acids chemical synthesis, benzoic acids chemistry, biological availability, blood pressure drug effects, carbachol antagonists and inhibitors, carbachol pharmacology, dogs, drug design, drug evaluation, preclinical, injections, intravenous, models, animal, molecular structure, stereoisomerism, structure activity relationship, time factors.

Ishida, S., A. Takeuchi, T. Azami, K. Sobue, H. Sasano, H. Katsuya, and J.A. Fisher (2007). **Cardiac output increases the rate of carbon monoxide elimination in hyperpneic but not normally ventilated dogs.** *Journal of Anesthesia* 21(2): 181-6. ISSN: 0913-8668.
Abstract: PURPOSE: The very high solubility of carbon monoxide (CO) in blood suggests that its elimination depends predominantly on ventilation and not perfusion. Nevertheless, hyperventilation is not used for CO elimination because of the adverse effects of hypocapnia. With isocapnic hyperpnea (IH), ventilation can be increased considerably without hypocapnia. This raises the issue of whether CO elimination is limited by perfusion during IH. We studied the effect of increasing cardiac output on t1/2, the half-time of decline of blood carboxyhemoglobin concentration ([COHb]), during normal ventilation (NV) and during IH. METHODS: After ethics approval was received, 13 pentobarbital-anesthetized ventilated dogs were exposed to CO to increase their [COHb]. They were then ventilated with NV or IH. At each level of ventilation, dogs were randomly assigned to treatment with dobutamine (to increase cardiac output) or to no dobutamine treatment. After the return of [COHb] to control levels, each dog was re-exposed to CO and treated with the same ventilatory mode, but the alternative inotropic treatment. RESULTS: Gas exchange, [COHb], and hemodynamic measures were recorded during the study. Cardiac index values in the IH group were 4.1 +/- 0.5 and 8.2 +/- 1.2 l.min(-1).m(-2) without and with dobutamine infusion, respectively. Dobutamine infusion was associated with a reduction in t1/2 from 20.3 +/- 3.6 to 16.9 +/- 2.4 min (P = 0.005) in the IH group, but no change in the NV group. CONCLUSION: These findings suggest that CO elimination during IH treatment is limited at least partly by pulmonary blood flow and may therefore be further augmented by increasing cardiac output.
Descriptors: carbon monoxide metabolism, carboxyhemoglobin metabolism, cardiac output physiology, hyperventilation physiopathology, respiratory physiological phenomena drug effects, cardiotonic agents pharmacology, dobutamine pharmacology, dogs, models, animal.

Ishizaka, T., A. Takahara, H. Iwasaki, Y. Mitsumori, H. Kise, Y. Nakamura, and A. Sugiyama (2008). **Comparison of electropharmacological effects of bepridil and sotalol in halothane-anesthetized dogs.** *Circulation Journal Official Journal of the Japanese Circulation Society* 72(6): 1003-11. ISSN: 1346-9843.
Abstract: BACKGROUND: Bepridil is known to have a multiple ion channel-blocking property in the heart, which has been applied for the treatment of atrial fibrillation and drug-

refractory ventricular tachyarrhythmias. In this study, the electro-pharmacological effects of bepridil were compared with those of dl-sotalol, a representative class III antiarrhythmic drug, using the halothane-anesthetized canine model. METHODS AND RESULTS: Cardiovascular and electrophysiological variables were measured under the halothane anesthesia. Intravenous administration of bepridil (0.3 mg/kg, n=4) delayed the intraventricular conduction and prolonged the ventricular effective refractory period, whereas dl-sotalol (0.3 mg/kg, iv, n=4) inhibited atrioventricular conduction and prolonged the atrial and ventricular effective refractory period. The additional administration of 10 times the higher dose of bepridil or dl-sotalol (ie, 3 mg/kg, iv, n=4 for each group) decreased blood pressure, suppressed ventricular contraction and sinus automaticity, and prolonged the atrial and ventricular effective refractory period and monophasic action potential duration, in addition to the effects of the low dose. CONCLUSIONS: The electropharmacological effects of bepridil and dl-sotalol were similar, although their potency for each cardiovascular variable varied significantly. These findings can be useful when selecting these drugs according to the pathophysiological condition of a patient.

Descriptors: adrenergic beta antagonists pharmacology, bepridil pharmacology, heart conduction system drug effects, sotalol pharmacology, vasodilator agents pharmacology, adrenergic beta antagonists blood, anesthetics, inhalation, atrioventricular node drug effects, bepridil blood, bundle of his drug effects, dogs, dose response relationship, drug, electrocardiography drug effects, halothane, models, animal, myocardial contraction drug effects, pacemaker, artificial, sinoatrial node drug effects, sotalol blood, vasodilator agents blood.

Iyer, R.A., B. Malhotra, S. Khan, J. Mitroka, S.J. Bonacorsi, S.C. Waller, J.K. Rinehart, and K. Kripalani (2003). **Comparative biotransformation of radiolabeled (14c)omapatrilat and stable-labeled (13c2)omapatrilat after oral administration to rats, dogs, and humans.** *Drug Metabolism and Disposition* 31(1): 67-75. ISSN: 0090-9556.

NAL Call Number: RM301.35.D78

Abstract: Omapatrilat, a novel vasopeptidase inhibitor, is under development for the treatment of hypertension and congestive heart failure. This study describes the comparative biotransformation of radiolabeled (14C)- and stable-labeled (13C2)omapatrilat after administration of single oral doses to rats, dogs, and humans. The metabolites were identified by a combination of methods including reduction, hydrolysis, and comparison of high performance liquid chromatography retention times with those of the synthetic standards. Urinary metabolites were further characterized by liquid chromatography tandem mass spectrometry analysis. Prominent metabolites identified in human plasma, which were also present in rat and dog plasma, were S-methyl omapatrilat and S-2-thiomethyl-3-phenylpropionic acid. Omapatrilat accounted for only a small portion of the extractable radioactivity in plasma in all three species. A portion of the plasma radioactivity was unextractable in all three species (27-53%). The majority of unextractable radioactivity in plasma was characterized after dithiothreitol reduction to be omapatrilat and (S)-2-thio-3-phenylpropionic acid, both apparently bound to plasma proteins by reversible disulfide bonds. The major human urinary metabolites were the amine hydrolysis product, diasteromeric sulfoxide of (S)-2-thiomethyl-3-phenylpropionic acid, acyl glucuronide of S-methyl omapatrilat, and S-methyl omapatrilat. The minor metabolites were acyl glucuronide of (S)-2-thiomethyl-3-phenylpropionic acid, L-cysteine mixed disulfide of omapatrilat, diastereomers of S-methyl sulfoxide of omapatri-

lat, and S-methyl omapatrilat ring sulfoxide. The metabolic profiles of dog and human urine were qualitatively similar whereas rat urine showed only metabolites arising from hydrolysis of omapatrilat. Unchanged omapatrilat was not found in rat, dog, or human urine samples indicating extensive metabolism in vivo.
Descriptors: pharmacology, comparative biotransformation, rat, dog, human, omapatrilat, novel vasopeptidase inhibitor, hypertension, congestive heart failure.

Jin, L., I.W. Chen, M. Chiba, and J.H. Lin (2003). **Interaction with indinavir to enhance systemic exposure of an investigational hiv protease inhibitor in rats, dogs and monkeys.** *Xenobiotica* 33(6): 643-654. ISSN: 0049-8254.
NAL Call Number: QD415.A1X4
Abstract: 1. The use of a beneficial interaction between indinavir and compound A, a potent investigational HIV protease inhibitor to enhance systemic exposure of compound A, was investigated. 2. When administrated alone, compound A underwent extensive hepatic first-pass metabolism in rats and monkeys, resulting in low oral bioavailability. 3. In vitro studies with liver microsomes revealed that compound A metabolism was mediated exclusively by CYP3A enzymes in rats, dogs and monkeys. Indinavir, which also was metabolized predominantly by CYP3A enzymes, extensively inhibited compound A metabolism in microsomes, whereas compound A showed weak inhibitory potency on indinavir metabolism. 4. Consistent with in vitro observations, co-administration of the two compounds resulted in a 17-fold increase in oral AUC of compound A in rats owing to the inhibition of metabolism of compound A by indinavir, whereas compound A did not affect indinavir metabolism as indicated by the unchanged indinavir AUC. Similarly, the systemic exposure of compound A in dogs and monkeys was increased substantially following oral co-administration with indinavir by 7- and > 50-fold, respectively. 5. Enhancement in compound A systemic exposure by indinavir in humans, as predicted based on the in vivo animal and in vitro human liver microsomal data, was confirmed in subsequent clinical studies.
Descriptors: digestive system, ingestion and assimilation, metabolism, pharmacology, extensive hepatic first pass metabolism.

Julian, L.D., Z. Wang, T. Bostick, S. Caille, R. Choi, M. DeGraffenreid, Y. Di, X. He, R.W. Hungate, J.C. Jaen, J. Liu, M. Monshouwer, D. McMinn, Y. Rew, A. Sudom, D. Sun, H. Tu, S. Ursu, N. Walker, X. Yan, Q. Ye, and J.P. Powers (2008). **Discovery of novel, potent benzamide inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) exhibiting oral activity in an enzyme inhibition ex vivo model.** *Journal of Medicinal Chemistry* 51(13): 3953-60.
NAL Call Number: RS402
Abstract: We report the discovery of potent benzamide inhibitors of 11beta-hydroxysteroid dehydrogenase (11beta-HSD1). The optimization and correlation of in vitro and in vivo metabolic stability will be described. Through modifications to our initial lead 2, we discovered pyridyl compound 13. This compound has a favorable pharmacokinetic profile across three species and showed a dose-dependent decrease in adipose 11beta-HSD1 activity in a monkey ex vivo pharmacodynamic model.
Descriptors: 11 beta hydroxysteroid dehydrogenase type 1 antagonists and inhibitors, benzamides administration and dosage, benzamides chemical synthesis, enzyme inhibitors

administration and dosage, enzyme inhibitors chemical synthesis, 11 beta hydroxysteroid dehydrogenase type 1 chemistry, 11 beta hydroxysteroid dehydrogenase type 1 metabolism, administration, oral, benzamides chemistry, benzamides metabolism, cell line, crystallography, x ray, dogs, enzyme inhibitors chemistry, enzyme inhibitors metabolism, macaca fascicularis, models, animal, models, molecular, molecular structure, rats, structure activity relationship.

Kador, P.F., K. Blessing, and M. Wyman (2003). **The results of combretastatin in galactose - fed dogs with diabetes - like proliferative retinopathy**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*
Abstract: Purpose: Combretastatin A-4 (CA4P) is a vascular targeting agent that has been reported to be capable of destroying newly formed capillary endothelial cells in growing vessels. The net effect of this drug has been to rapidly shut off blood flow in newly growing vessels and, as a result, regress neovascularization. The purpose of this study was to determine whether retinal neovascularization which results in altered retinal vessel blood flow and retinal permeability in the long-term galactose-fed dog can be halted with CA4P. Methods: All experiments conform to the ARVO Resolution on the Use of Animals in Research and NIH ACUC Guidelines. Eight beagles fed 30% galactose diet for 80-104 months and four age-matched control dogs were surgically made aphakic. Following recovery the dogs were divided into two groups each containing 4 galactose-fed dogs and 2 age-matched controls dogs with each group receiving CA4P either as sub-Tenon's injections administered at the corneoscleral junction or intravitreal injections. Six weeks after initial CA4P treatment all dogs also received systemic (IV) injections of CA4P. The extent of neovascularization and affect of CA4P administration were monitored by fluorescein angiography and color and monochromatic fundus photography at 2-week intervals. Results: Although CA4P was well tolerated by the healthy eyes of the control animals its administration to galactose-fed dogs was associated with corneal edema and increases in IOP after sub-Tenon's and intraocular injections. All galactose-fed dogs demonstrated retinal neovascular lesions and these were not ameliorated by either sub-Tenon's, intravitreal or systemic CA4P administration. Conclusions: Neovascularization in this animal model progresses over a period of years similar to that observed clinically. The failure of CA4P to ameliorate neovascularization suggests that chronic, long-term administration is required to destroy the slowly growing retinal endothelial cells.
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, sense organs, sensory reception, aphakia, eye disease, diabetes like proliferative retinopathy, endocrine disease, pancreas, metabolic disease, retinal blood vessel blood flow, retinal neovascularization.

Kaewsakhorn, T., M. Gower, W. Kisseberth, C. Capen, M. Calverley, and N. Inpanbutr (2004). **Effects of calcitriol and medium chain triglyceride (mct) on cell growth of the canine transitional cell carcinoma of the urinary bladder (tcc) in vitro**. *FASEB Journal* 18(4-5): Abst. 68.8. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: calcitriol , cell biology, cell proliferation, pharmacology, tumor biology, bladder

transitional cell carcinoma, neoplastic disease, urologic disease, therapy, western blot, genetic techniques, laboratory techniques, drug regimen.

Kangasniemi, M., R.J. Stafford, R.E. Price, E.F. Jackson, and J.D. Hazle (2003). **Dynamic gadolinium uptake in thermally treated canine brain tissue and experimental cerebral tumors.** *Investigative Radiology* 38(2): 102-107. ISSN: 0020-9996.

Abstract: RATIONALE AND OBJECTIVES: Thermal coagulation of cerebral tumors induces reactive changes within adjacent brain tissue, which appear as Gd-DTPA enhancement in MR images. This makes assessment of therapeutic success difficult to establish radiographically because the reactive changes can mimic residual tumor. Dynamic Gd-DTPA uptake curves in reactive tissue and tumor were investigated to assess the utility of contrast enhanced (CE)-dynamic MRI to distinguish reactive changes from residual tumor in a canine model. MATERIALS AND METHODS: Cerebral thermal necrosis was induced using a 980 nm laser in 11 dogs with intracerebral transmissible venereal tumors (TVTs). A fast spin-echo T1-weighted imaging sequence was used for CE-dynamic MRI. Gd-DTPA uptake data were acquired with 10-second temporal resolution and for untreated TVTs for reactive tissue using a sigmoidal-exponential model. RESULTS: Characteristic gadolinium uptake curves were measured and characterized for reactive brain tissue, and untreated and treated TVTs. Both early and delayed dynamic responses were significantly different in reactive brain tissue compared with TVT. CONCLUSION: Reactive thermal changes in otherwise normal brain tissue can be distinguished from residual tumor after cerebral thermal therapy using CE -dynamic MRI.

Descriptors: nervous system, neural coordination, pharmacology, tumor biology, cerebral thermal necrosis, nervous system disease, intracerebral transmissible venereal tumor, neoplastic disease, radiotherapy, contrast enhanced dynamic magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, fast spin echo t1 weighted imaging, sigmoidal exponential model, mathematical and computer techniques, thermal coagulation therapy, therapeutic and prophylactic techniques, reactive thermal change.

Kast, R., H. Schirok, S. Figueroa Perez, J. Mittendorf, M.J. Gnoth, H. Apeler, J. Lenz, J.K. Franz, A. Knorr, J. Hutter, M. Lobell, K. Zimmermann, K. Munter, K.H. Augstein, H. Ehmke, and J.P. Stasch (2007). **Cardiovascular effects of a novel potent and highly selective azaindole-based inhibitor of Rho-kinase.** *British Journal of Pharmacology* 152(7): 1070-80. ISSN: 0007-1188.

NAL Call Number: 396.8 B77

Abstract: BACKGROUND AND PURPOSE: Rho-kinase (ROCK) has been implicated in the pathophysiology of altered vasoregulation leading to hypertension. Here we describe the pharmacological characterization of a potent, highly selective and orally active ROCK inhibitor, the derivative of a class of azaindoles, azaindole 1 (6-chloro-N4-{3,5-difluoro-4-[(3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]-phenyl}pyrimidine-2,4-diamine). EXPERIMENTAL APPROACH: Pharmacological characterization of azaindole 1 was performed with human recombinant ROCK in vitro. Vasodilator activity was determined using isolated vessels in vitro and different animal models in vivo. KEY RESULTS: This compound inhibited the ROCK-1 and ROCK-2 isoenzymes with IC50 s of 0.6 and 1.1 nM in an

ATP-competitive manner. Although ATP-competitive, azaindole 1 was inactive against 89 kinases (IC50>10 microM) and showed only weak activity against an additional 21 different kinases (IC50=1-10 microM). Only the kinases TRK und FLT3 were inhibited by azaindole 1 in the sub-micromolar range, albeit with IC50 values of 252 and 303 nM, respectively. In vivo, azaindole 1 lowered blood pressure dose-dependently after i.v. administration in anaesthetized normotensive rats. In conscious normotensive and spontaneously hypertensive rats azaindole 1 induced a dose-dependent decrease in blood pressure after oral administration without inducing a significant reflex increase in heart rate. In anaesthetized dogs, azaindole 1 induced vasodilatation with a moderately elevated heart rate. CONCLUSIONS AND IMPLICATIONS: Azaindole 1 is representative of a new class of selective and potent ROCK inhibitors and is a valuable tool for the elucidation of the role of ROCK in the cardiovascular system.

Descriptors: cardiovascular system drug effects, diamines pharmacology, protein kinase inhibitors pharmacology, pyrimidines pharmacology, rho associated kinases antagonists and inhibitors, administration, oral, apoptosis regulatory proteins antagonists and inhibitors, apoptosis regulatory proteins genetics, apoptosis regulatory proteins metabolism, binding sites drug effects, blood pressure drug effects, calcium calmodulin dependent protein kinases antagonists and inhibitors, calcium calmodulin dependent protein kinases genetics, calcium calmodulin dependent protein kinases metabolism, cells, cultured, computer simulation, dogs, dose response relationship, drug, injections, intravenous, mice, models, animal, models, molecular, organ culture techniques, phosphorylation, polymerase chain reaction methods, protein kinase inhibitors administration and dosage, protein kinase inhibitors chemistry, rabbits, rats, rats, inbred shr, rats, wistar, recombinant proteins antagonists and inhibitors, recombinant proteins genetics, recombinant proteins metabolism, time factors, vasodilator agents administration and dosage, vasodilator agents chemistry, vasodilator agents pharmacology, rho associated kinases genetics, rho associated kinases metabolism.

Kawase, A., T. Ikeda, K. Nakazawa, T. Ashihara, T. Namba, T. Kubota, K. Sugi, and H. Hirai (2003). **Widening of the excitable gap and enlargement of the core of reentry during atrial fibrillation with a pure sodium channel blocker in canine atria.** *Circulation* 107(6): 905-910. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8

Abstract: Background: This study aimed to assess the effects of pilsicainide, a pure sodium channel blocker, on electrophysiological action and wavefront dynamics during atrial fibrillation (AF). Methods and Results: In a newly developed model of isolated, perfused, and superfused canine atria (n=12), the right and left endocardia were mapped simultaneously by use of a computerized mapping system. AF was induced with 1 to 5 mumol/L acetylcholine. The antifibrillatory actions of pilsicainide on AF cycle length (AFCL), refractory period (RP), conduction velocity (CV), excitable gap (EG), and the core of the mother rotor were studied. The RP was defined as the shortest coupling interval that could capture the fibrillating atrium. The EG was estimated as the difference between the AFCL and RP. At baseline, multiple wavefronts were observed. After 2.5 mug/mL infusion of pilsicainide, all preparations showed irregular activity, and AF was terminated in 2 preparations. The AFCL and RP were prolonged, and CV was decreased significantly. The EG was widened (147%; P<0.01), and the core perimeter was increased (100%; P<0.01). Increasing the dosage either terminated AF

(6 preparations) or converted to organized activity (ie, atypical atrial flutter) (4 preparations). On the maps, all "unorganized" AFs were terminated with the excitation of the core of the mother rotor by an outside wavefront, whereas in preparations with atrial flutter, pilsicainide did not terminate its activity. Conclusions: Widening of the EG by pilsicainide facilitates the excitation of the core of the mother rotor, leading to the termination of AF. In some experiments, pilsicainide converts AF to persistent atrial flutter.
Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial fibrillation, heart disease, drug therapy, pathology, electrophysiology, clinical techniques, conduction velocity, cycle length, excitable gap widening, reentry core enlargement, refractory period, wavefront dynamics.

Kent, M.S., B.R. Madewell, G. Dank, R. Dick, S.D. Merajver, and G.J. Brewer (2004). **An anticopper antiangiogenic approach for advanced cancer in spontaneously occurring tumors using tetrathiomolybdate: a pilot study in a canine animal model.** *Journal of Trace Elements in Experimental Medicine* 17(1): 9-20. ISSN: 0896-548X.
NAL Call Number: QP534.J68
Abstract: In this pilot study, 13 dogs of various breeds and ages with a variety of advanced tumors were treated with the antiangiogenic copper complexing drug tetrathiomolybdate. Dose escalations were performed to determine the safe and effective dose in dogs. The study was designed to last for a 6-month period for each dog entered. Dogs were examined weekly for the first 3 months and then every other week for the next 3 months. Complete blood count, serum biochemistry panel, and measurement of serum ceruloplasmin (Cp) content were conducted at each visit to monitor response to drug administration. Serum Cp was used as a surrogate marker of copper status. The owner reported toxicity at each visit. The dog was examined for physical abnormalities. Tumor measurements were completed every 2 weeks using direct measurements of the tumor with calipers in three planes or by direct measurements of the tumor using radiographic or ultrasonographic images in two planes. Tumor response was evaluated only after dogs achieved a 4-week reduction in their serum Cp content. Tumor responses were defined as either disease stabilization or reduction in tumor volume. Nine dogs achieved Cp reduction. Of those dogs, five had no response to treatment, whereas four dogs had tumor responses after Cp reduction, characterized as either disease stabilization or reduction in tumor volume, for the remainder of the study period. There was only mild self-limiting toxicity with use of the drug.
Descriptors: pharmacology, veterinary medicine, medical sciences, advanced cancer, neoplasms, neoplastic disease, drug therapy, spontaneously occurring tumor.

Kerbaul, F., B. Rondelet, S. Motte, P. Fesler, I. Hubloue, P. Ewalenko, R. Naeije, and S. Brimioulle (2004). **Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure.** *Critical Care Medicine* 32(4): 1035-40. ISSN: 0090-3493.
Abstract: OBJECTIVE: A transient increase in pulmonary arterial (PA) pressure can persistently depress right ventricular (RV) contractility. We investigated the effects norepinephrine and dobutamine on RV-PA coupling in this model of RV failure. DESIGN: Prospective, controlled, randomized animal study. SETTING: University research laboratory. SUBJECTS: Twenty-two anesthetized dogs. INTERVENTIONS: Animals underwent transient (90-min) PA constriction to induce persistent RV failure. They were randomly assigned to control,

norepinephrine, or dobutamine group. Norepinephrine was administered at 0.1 and 0.5 microg x kg x min or dobutamine at 5 and 10 microg x kg x min. MEASUREMENTS AND MAIN RESULTS: We measured PA distal resistance and proximal elastance by pressure-flow relationships and vascular impedance. We also measured RV contractility by the end-systolic pressure-volume relationship (Ees), PA effective elastance by the end-diastolic to end-systolic relationship (Ea), and RV-PA coupling efficiency by the Ees/Ea ratio. The transient PA constriction persistently increased PA resistance and elastance, increased Ea from 0.8+/-0.1 to 2.7+/-0.3 mmHg/mL, decreased Ees from 1.1+/-0.1 to 0.5+/-0.1 mm Hg/mL, and decreased Ees/Ea from 1.2+/-0.1 to 0.2+/-0.1. Norepinephrine restored arterial pressure, increased RV contractility, and increased but did not normalize RV-PA coupling and cardiac output. Dobutamine restored arterial pressure, markedly increased RV contractility, and normalized RV-PA coupling and cardiac output. Compared with norepinephrine, dobutamine decreased PA resistance and elastance and increased RV contractility and RV-PA coupling. CONCLUSIONS: A transient increase in PA pressure persistently worsens PA hemodynamics, RV contractility, RV-PA coupling, and cardiac output. Dobutamine restores RV-PA coupling and cardiac output better than norepinephrine because of its more pronounced inotropic effect.
Descriptors: animal model, pulmonary arterial (PA) pressure, right ventricular (RV) contractility, cardiac output, norepinephrine, dobutamine.

Kim, J.T., K.Y. Rhee, J.H. Bahk, S.H. Do, Y.J. Lim, H. Ko, and K.H. Lee (2003). **Continuous mixed venous oxygen saturation, not mean blood pressure, is associated with early bupivacaine cardiotoxicity in dogs.** *Canadian Journal of Anesthesia* 50(4): 376-381. ISSN: 0832-610X.

Abstract: Purpose: To investigate changes of continuous mixed venous oxygen saturation (cSvO2) and mean arterial blood pressure (MBP) in dogs with bupivacaine-induced cardiac depression. Methods: Bupivacaine was infused into pentobarbital-anesthetized mongrel dogs (n=8) at a rate of 0.5 mgcntdotkg-1cntdotmin-1 until the MBP was 40 mmHg or less (end of bupivacaine infusion; BIE). The infusion time was divided into the early period, first 30 min of bupivacaine infusion and the late period, which was from 30 min of bupivacaine infusion until BIE. cSvO2 was monitored using a fibreoptic pulmonary artery catheter, and MBP and cardiac output (CO) were measured every ten minutes after the initiation of bupivacaine infusion. Arterial blood gas, serum electrolyte and bupivacaine concentration were measured simultaneously. The relationships between CO and cSvO2, and of CO vs MBP were compared by regression analysis in the early and late periods. Results: The Pearson's correlation coefficients between CO and cSvO2 were 0.782 (P=2.1X10-7) in the early period and 0.824 (P=1.3X10-6) in the late period. The correlation coefficients between CO and MBP were 0.019 (P=0.921) in the early period and 0.799 (P=4.8X10-6) in the late period. Conclusions: cSvO2, but not MBP, is associated with CO changes in bupivacaine-induced cardiac depression during the early period of bupivacaine intoxication. Decrease of MBP with low cSvO2 observed during the late period might imply severe cardiac depression induced by bupivacaine infusion.
Descriptors: cardiovascular system, transport and circulation, pharmacology, toxicology, bupivacaine induced cardiac depression, heart disease, toxicity, continuous mixed venous oxygen saturation, bupivacaine induced cardiotoxicity association, mean blood pressure.

Kimura, K., M. Tabo, K. Mizoguchi, A. Kato, M. Suzuki, Z. Itoh, S. Omura, and H. Takanashi (2007). **Hemodynamic and electrophysiological effects of mitemcinal (GM-611), a novel prokinetic agent derived from erythromycin in a halothane-anesthetized canine model.** *Journal of Toxicological Sciences* 32(3): 231-9. ISSN: 0388-1350.
NAL Call Number: RA1190
Abstract: Mitemcinal (GM-611) is a novel erythromycin-derived prokinetic agent that acts as an agonist at the motilin receptor. We investigated the QT-prolonging effects of mitemcinal using a halothane-anesthetized canine model. Intravenous administration of mitemcinal at doses of more than 8.3 mg/kg per 10 min significantly prolonged the QT interval corrected by Fridericia's corrections. Mitemcinal exhibited a bradycardiac effect and produced significantly greater prolongation in monophasic action potential duration (MAP(90)) at sinus rhythm compared with MAP(90) at pacing and showed reverse use-dependent prolongation of repolarization, suggesting that the negative chronotropic effect of mitemcinal potentiates the prolongation of the repolarization period. A technique using MAP/pacing electrodes allowed measurements of both MAP(90) and effective refractory period (ERP) simultaneously at the same ventricular site. Although mitemcinal slightly prolonged the MAP(90(CL400)) and ERP in comparison with the control group at the dose of 25 mg/kg per 10 min, the terminal repolarization period, the difference between MAP(90(CL400)) and ERP, did not increase suggesting the absence of a proarrhythmic effect even with a 7000-fold for the therapeutic blood concentration as free level. The electrophysiological results from mitemcinal in this study indicate that the risk of serious arrhythmia such as torsades de pointes, a major clinical concern related to QT interval prolongation, might be low.
Descriptors: blood pressure drug effects, erythromycin analogs and derivatives, gastrointestinal agents toxicity, gastrointestinal motility drug effects, heart rate drug effects, long qt syndrome chemically induced, torsades de pointes chemically induced, ventricular function, left drug effects, action potentials drug effects, anesthesia, general, anesthetics, inhalation, cardiac pacing, artificial, cisapride toxicity, dogs, dose response relationship, drug, electrocardiography, erythromycin administration and dosage, erythromycin blood, erythromycin toxicity, gastrointestinal agents administration and dosage, gastrointestinal agents blood, halothane, infusions, intravenous, long qt syndrome physiopathology, models, animal, risk assessment, time factors, torsades de pointes physiopathology, ventricular pressure drug effects.

Kita, T., K. Kubo, I. Narushima, S. Matsumura, Y. Yonetani, and T. Nakashima (1996). **Behavioral effects and role of endothelin in a canine subarachnoid model**. *Japanese Journal of Pharmacology* 71(SUPPL. 1): 91P. ISSN: 0021-5198.
Descriptors: behavior, cardiovascular system, transport and circulation, endocrine system, chemical coordination and homeostasis, nervous system, neural coordination, animal model, basilar artery caliber, behavioral effect, cerebral vasospasm, endocrine system, endothelin 1, meeting poster, meningeal sign, nervous system disease, severe ataxia, subarachnoid hemorrhage, vascular disease

Kucukhuseyin, C. (2003). **Cardiovascular effects of intravenous pentazocine and cyclazocine in conscious, curarized-conscious, and anesthetized dogs.** *Journal of Basic and Clinical Physiology and Pharmacology* 14(3): 235-255. ISSN: 0792-6855.

Abstract: The cardiovascular effects of intravenous pentazocine and cyclazocine in dogs were studied under conscious, curarized-conscious (paralyzed by gallamine), and anesthetized states. In the conscious state, blood pressure and heart rate were dose-dependently increased by pentazocine (1, 2, 3 mg/kg) and to a lesser extent by cyclazocine (0.3 mg/kg). In all subsequent experiments on dogs, the results were obtained using 3 mg/kg pentazocine and 0.3 mg/kg cyclazocine. Pentazocine accelerated breathing, peaking at about 10 min, whereas cyclazocine reduced breathing to a minimum in 1 min, followed by a gradual recovery thereafter. In the curarized-conscious state, the blood pressure response to pentazocine was biphasic, namely an initial decrease followed by an increase; chronotrophic activity was stimulated. Pretreatment with either ganglionic or alpha andrenergic blocking agents not only significantly antagonized the pressory responses to the drug but also potentiated the initial decreases in blood pressure and unmasked a bradycardic component, but these parameters were not altered by 0.3 mg/kg naxalone. In open-chest anesthetized dogs, blood pressure, heart rate, contractility, and mean peripheral vascular resistance were simultaneously decreased by both pentazocine and cyclazocine, initially accompanied by increases in aortic blood flow. During the later stages of drug action, only the blood pressure and contractility were increased above control levels (biphasic effect). A comparison of blood pressure and heart rate responses to pentazocine in dogs kept under differing experimental conditions revealed that conscious dogs were more sensitive than curarized conscious and anesthetized animals to pentazocine action. In isolated guinea pig atria, the effect of adrenaline (0.1, 0.3, or 1 mg/mL) on the spontaneous breathing rate was significantly augmented by 10 mg/mL pentazocine ($p<0.02$ for 0.3 g/mL; $p<0.01$ for 0.1 g/mL adrenaline). In dogs, however, adrenaline (1 mg/kg)-induced increases in heart contractility, aortic blood flow, and blood pressure remained almost unaltered in the presence of pentazocine. We concluded that the above mentioned cardiovascular responses to pentazocine and cyclazocine are a consequence of the sum of the two following opposing effects: (i) an indirect reflex activation of sympathetic neuromediation in the periphery, and (ii) a direct membrane effect on the heart leading to bradycardia and a depression in myocardial contractility.
Descriptors: cardiovascular system, transport and circulation, pharmacology, curarization, experimental surgical techniques, laboratory techniques, blood pressure, conscious state, heart rate.

Kumagai, K., H. Nakashima, N. Gondo, and K. Saku (2003). **Antiarrhythmic effects of jtv-519, a novel cardioprotective drug, on atrial fibrillation/flutter in a canine sterile pericarditis model.** *Journal of Cardiovascular Electrophysiology* 14(8): 880-884. ISSN: 1045-3873.
Abstract: Introduction: A new cardioprotective drug, JTV-519, blocks Na+ current and inwardly rectifying K+ current and inhibits Ca2+ current. However, its role in atrial electrophysiology is unknown. We investigated the antiarrhythmic effects of JTV-519 on atrial fibrillation/flutter in the canine sterile pericarditis model. Methods and Results: In nine dogs with sterile pericarditis, 38 episodes of sustained (>30 sec) atrial fibrillation (8 dogs) and 24 episodes of sustained atrial flutter (7 dogs) were induced by rapid atrial pacing. When atrial fibrillation or atrial flutter was sustained >15 minutes, it was cardioverted and reinduced. The inducibility of atrial fibrillation/flutter, the atrial effective refractory period, and the intra-atrial conduction time were compared before and after the continuous infusion of JTV-519 (0.03 mg/kg/min). JTV-519 significantly decreased the mean number of sustained

atrial fibrillation episodes (from 4.2+-2.9 to 0+-0, P<0.01). In contrast, atrial flutter was still inducible in 4 dogs after JTV-519 (from 2.7+-2.5 to 1.6+-2.1, P=NS). JTV-519 significantly prolonged effective refractory period (from 123+-18 to 143+-14 msec, from 127+-18 to 151+-12 msec, and from 132+-13 to 159+-9 msec at basic cycle lengths of 200, 300, and 400 msec, respectively, P<0.01), but it did not affect the intra-atrial conduction time (from 47+-11 msec to 48+-11 msec, P=NS). Conclusion: JTV-519 had significant protective effects on atrial fibrillation in the canine sterile pericarditis model, mainly by increasing effective refractory period, suggesting that it may have potential as a novel antiarrhythmic agent for atrial fibrillation.

Descriptors: cardiovascular system, transport and circulation, pharmacology, atrial fibrillation, heart disease, drug therapy, atrial flutter, heart disease, drug therapy, sterile pericarditis, electrophysiology, clinical techniques, atrial effective refractory period, calcium ion current, intra atrial conduction time, inwardly rectifying potassium ion current, sodium ion current.

Leach, J.K., E. Patterson, and E.A. O'rear (2004). **Encapsulation of a plasminogen activator speeds reperfusion, lessens infarct and reduces blood loss in a canine model of coronary artery thrombosis**. *Thrombosis and Haemostasis* 91(6): 1213-1218. ISSN: 0340-6245.

Abstract: In the present study, a polymer-encapsulated plasminogen activator was investigated as an alternative to restore blood flow more effectively than free plasminogen activator. While current fibrinolytic agents have limited efficacy, attributable to delayed onset of sustained reperfusion and bleeding complications, encapsulated plasminogen activators have shown promise in addressing these shortcomings. A polymer-encapsulated plasminogen activator could offer an effective formulation with a prolonged shelf-life. In this study, coronary artery thrombosis was produced in the anesthetized dog by the injection of thrombin + whole blood, and then one of five randomly selected formulations was administered intravenously: saline, blank microcapsules, free streptokinase (FREE SK), streptokinase and blank microcapsules (FREE SK + BLANK), or streptokinase entrapped in polymer microcapsules (MESK). MESK significantly accelerated the time to reperfusion compared to FREE SK or FREE SK + BLANK. Additionally, substantial reductions were observed in residual clot mass, infarct mass, reocclusion episodes, fibrinogen depletion and blood loss with MESK compared to FREE SK. The results of this study demonstrate that MESK accelerates thrombolysis and the restoration of blood flow compared to identical dosages of FREE SK while also reducing systemic fibrinogenolysis and blood loss. Microencapsulation may produce an improved dosage form for restoring arterial blood flow and reducing bleeding complications with thrombolytic therapy.

Descriptors: cardiovascular system, transport and circulation, pharmacology, coronary artery thrombosis, heart disease, vascular disease, therapy .

Lee, B.H., H.W. Seo, and S.E. Yoo (2004). **Cardioprotective effects of (2s,3r,4s)-n'-benzyl-n"-cyano-n-(3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2h-benzopyran-4-yl)-guanidine (kr-31372) in rats and dogs.** *Pharmacology* 70(2): 74-82. ISSN: 0031-7012.

NAL Call Number: RM1.P473

Abstract: The cardioprotective effects of (2S,3R,4S)-N'-benzyl-N"-cyano-N-(3,4-dihydro-2-dimethoxymethyl-3-hydroxy-2-methyl-6-nitro-2H-benzopyran-4-yl)-guanidine (KR-31372)

were evaluated against ischemic/reperfusion injury in isolated rat hearts in vitro and in anesthetized rats and dogs in vivo. In isolated perfused rat hearts subjected to a 30-min global ischemia/30-min reperfusion, KR-31372 (1-10 muM) significantly improved severe contracture (end-diastolic pressure and time to contracture), markedly reduced reperfusion lactate dehydrogenase release, and enhanced the recovery of reperfusion contractile function (left ventricular developed pressure and double product) in a concentration-dependent manner compared with the vehicle-treated group. In anesthetized rats subjected to a 45-min coronary occlusion and a 90-min reperfusion, intravenous KR-31372 dose-dependently reduced infarct size from 58.6% to 48.5, 48.1 and 39.6% at 0.3, 1.0 and 3.0 mg/kg, respectively ($p<0.05$). In anesthetized beagle dogs that underwent a 1.5-hour occlusion followed by a 5-hour reperfusion, KR-31372 (2 mg/kg, i.v.) markedly reduced infarct size from 57.0% in controls to 28.0% ($p<0.05$). The cardioprotective effects of KR-31372 on contractile function in globally ischemic rat hearts and on reperfusion injury in anesthetized rats were significantly reversed by pretreatment with selective adenosine triphosphate-sensitive potassium (KATP) channel blockers, sodium 5-hydroxydecanoate and glibenclamide. Taken together, these results indicate that KR-31372 possesses potent cardioprotective effects in rats and dogs and its effects may be mediated by activation of mitochondrial KATP channels.
Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemia, reperfusion injury, vascular disease, drug therapy, pathology, cardioprotection, double product, end diastolic pressure, left ventricular developed pressure, severe contracture.

Lee, R.S., C.S. Kuhr, G.E. Sale, E. Zellmer, W.J. Hogan, R. Storb, and M.T. Little (2003). **Fty720 does not abrogate acute graft-versus-host disease in the dog leukocyte antigen-nonidentical unrelated canine model.** *Transplantation* 76(8): 1155-1158. ISSN: 0041-1337.
NAL Call Number: QP89.T73
Abstract: Background. Acute graft-versus-host disease (GVHD) remains a significant impediment to successful hematopoietic stem-cell transplantation (HSCT). Here, we examined the effectiveness of 2-amino-2-(2-(4-octylphenyl)ethyl)-1,3-propanediol hydrochloride (FTY720), an immunosuppressant that retraffics activated lymphocytes to secondary lymphoid organs, for the treatment of acute GVHD in an established dog leukocyte antigen-nonidentical unrelated canine HSCT model. Methods. Dogs were given HSCT after conditioning with 920 cGy total body irradiation. The dogs received methotrexate 0.4 mg/kg/day on days 1, 3, 6, and 11 and FTY720 (5 mg/kg/day orally) after developing GVHD. Results. Five of six dogs achieved engraftment, developed acute GVHD, and were treated with FTY720. FTY720 resulted in a profound decrease in lymphocytes and a temporary mitigation of clinical GVHD; however, GVHD recurred in all dogs. Four of five dogs were euthanized because of severe GVHD and the fifth because of severe inanition associated with moderate GVHD. Conclusions. Compared with controls, treatment of GVHD with FTY720 did not control this complication or significantly increase survival.
Descriptors: blood and lymphatics, transport and circulation, methods and techniques, pharmacology, acute graft vs host disease, immune system disease, hematopoietic stem cell transplantation, laboratory techniques, dog leukocyte antigen nonidentical unrelated donor, engraftment .

Lentz, K.A., M. Quitko, D.G. Morgan, J.E.J. Grace, C. Gleason, and P.H. Marathe (2007). **Development and validation of a preclinical food effect model.** *Journal of Pharmaceutical Sciences* 96(2): 459-72. ISSN: 0022-3549.
NAL Call Number: 396.8 J825
Abstract: A preclinical canine model capable of predicting a compound's potential for a human food effect was developed. The beagle dog was chosen as the in vivo model. A validation set of compounds with known propensities for human food effect was studied. Several diets were considered including high-fat dog food and various quantities of the human FDA meal. The effect of pentagastrin pretreatment was also investigated. The high-fat dog food did not predict human food effect and was discontinued from further evaluation. The amount of FDA meal in the dog was important in the overall prediction of the magnitude of human food effect. Fed/fasted Cmax and AUC ratios using a 50-g aliquot of the FDA meal in the dog were in the closest qualitative agreement to human data. Pentagastrin pretreatment did not affect the AUC in the fed state, but increased the fasted AUC for weakly basic compounds. Pentagastrin pretreatment and a 50-g aliquot of the FDA meal in the dog predicted the human food effect for a validation set of compounds. This model, which is intended for compound screening, will be helpful for determining food effect as a liability when compounds progress from discovery to clinical development. Copyright (c) 2006 Wiley-Liss, Inc.
Descriptors: dietary fats, drug evaluation, preclinical methods, food drug interactions, models, animal, pentagastrin pharmacology, biological availability, dogs, hiv protease inhibitors pharmacokinetics, hydroxymethylglutaryl coa reductase inhibitors pharmacokinetics, oligopeptides pharmacokinetics, pravastatin pharmacokinetics, pyridines pharmacokinetics.

Lian, X.Y. and J.L. Stringer (2004). **Inhibition of aconitase in astrocytes increases the sensitivity to chemical convulsants**. *Epilepsy Research* 60(1): 41-52. ISSN: 0920-1211.
Descriptors: behavior, nervous system, neural coordination, pharmacology, epilepsy, nervous system disease, neuronal damage, injury, nervous system disease, seizure, wet dog shakes, nervous system disease, drug induced, etiology, pathology, immunohistochemistry, immunologic techniques, laboratory techniques, silver staining, genetic techniques, chemical convulsant sensitivity.

Liu, J.C., P.K. Kao, P. Chan, Y.H. Hsu, C.C. Hou, G.S. Lien, M.H. Hsieh, Y.J. Chen, and J.T. Cheng (2003). **Mechanism of the antihypertensive effect of stevioside in anesthetized dogs.** *Pharmacology* 67(1): 14-20. ISSN: 0031-7012.
NAL Call Number: RM1.P473
Abstract: Stevioside is a sweet-tasting glycoside isolated from the leaves of Stevia rebaudiana. It has been used as a noncaloric sugar substitute in Japan and Brazil for decades. Previous studies have shown that it lowered blood pressure in spontaneously hypertensive rats by intravenous injection. This study was designed to evaluate the hypotensive effect of stevioside in dogs and to define the underlying mechanism. After nasogastric administration of stevioside powder (200 mg/kg), the blood pressure of healthy mongrel dogs began to significantly decrease at 60 min and returned to baseline level at 180 min. The reduction of blood pressure was more rapid (at 5-10 min) and effective after intravenous injection. However, no significant change of blood pressure was noted after injection through left vertebral artery, implicating that the hypotensive effect is not related to the central nervous system. Stevioside

also showed significant hypotensive effects in renal hypertensive dogs, in a dose-dependent manner. In cultured rat aortic smooth muscle cells (A7r5 cell line), stevioside can dose-dependently inhibit the stimulatory effects of vasopressin and phenylephrine on intracellular Ca2+ in a calcium-containing medium. However, no intracellular Ca2+ inhibitory effect was observed in calcium-free medium, implicating that stevioside may inhibit the Ca2+ influx from extracellular fluid. Our present data show that stevioside did not influence the calcium ionophore (A23187) induced Ca2+ influx, indicating that the antagonistic effect was through Ca2+ channels. This study confirmed that stevioside is an effective antihypertensive natural product, and its hypotensive mechanism may be probably due to inhibition of the Ca2+ influx.

Descriptors: cardiovascular system, transport and circulation, pharmacology, hypertension, vascular disease, drug therapy, hypotension, drug therapy, blood pressure, calcium ion influx.

Lurie, F., B. Driessen, J.S. Jahr, R. Reynoso, and R.A. Gunther (2003). **Validity of arterial and mixed venous oxygen saturation measurements in a canine hemorrhage model after resuscitation with varying concentrations of hemoglobin-based oxygen carrier.** *Anesthesia and Analgesia* 96(1): 46-50. ISSN: 0003-2999.

Abstract: In this study, we evaluated the validity of saturation measurements in mixed venous and arterial blood during posthemorrhagic anemia and resuscitation with varying levels of hemoglobin-based oxygen carrier (Hemoglobin glutamer-200 (bovine); Oxyglobin(R) (Hb-200)). Nineteen anesthetized, splenectomized, mixed-breed dogs were anesthetized (two were excluded from the data because they did not survive the exsanguination, supporting the validity of the model). Their pulmonary arteries were cannulated with the Abbott QVUE Oximetrix 3 catheter. An 18-gauge catheter was placed in the femoral artery, and a reusable Nellcor probe was applied to the tongue. Mixed venous and arterial samples were drawn at baseline, after 40% hemorrhage (to keep arterial pressure at 50 mm Hg), and postresuscitation with 30 mL/kg of 6% hetastarch in lactated Ringer's solution (n=4), 10 mL/kg of Hb-200, 20 mL/kg of hetastarch (n=6), 20 mL/kg of Hb-200, and 10 mL/kg of hetastarch (n=7). Samples were compared with oxygen content from the LEXO2CON-K oxygen analyzer, and oxygen content was calculated for all values from the monitors. Results were compared by using analysis of variance. There was good correlation (0.97gtoreqrgtoreq0.92) for the measured versus calculated hemoglobin oxygen saturation values at baseline. After resuscitation, the correlation between calculated and measured values of oxygen content was significantly smaller for all tested instruments. The values of oxygen content calculated from the oxygen saturation monitor and from the oximetric pulmonary artery can deviate by as much as 20% from directly measured values. We conclude that the administration of this oxygen therapeutic may interfere with the values of some monitors.

Descriptors: blood and lymphatics, transport and circulation, pharmacology, posthemorrhagic anemia, blood and lymphatic disease, resuscitation, clinical techniques, therapeutic and prophylactic techniques, oxygen saturation, arterial, mixed venous, validity .

Mano, Y., T. Usui, and H. Kamimura (2004). **Pharmacokinetics of ym466, a new factor xa inhibitor, in rats and dogs**. *European Journal of Drug Metabolism and Pharmacokinetics* 29(1): 7-13. ISSN: 0378-7966.

NAL Call Number: RM301.E8

Abstract: The pharmacokinetics of YM466, a selective inhibitor for factor Xa, was investigated after single intravenous and oral dosing to rats and dogs. After i.v. dosing, plasma YM466 concentration declined in a bi-phasic manner with a terminal elimination half-life of 1.4 h in rats and 0.8 h in dogs. Total plasma clearance values were 884 and 1212 ml/h/kg in rats and dogs, respectively. After oral dosing, plasma YM466 concentrations reached maximum within 2 h and increased in a dose-proportional manner in rats while increase was nonlinear in dogs. The absolute bioavailability of YM466 was 2.7 - 4.5 % in rats, almost constant regardless of the dose levels investigated, while it was 6.9 - 24.6 % in dogs, indicating nonlinear pharmacokinetics. The plasma protein binding of YM466 was 54.7 - 56.5 % in rats and 45.2 - 49.0 % in dogs and almost constant regardless of the concentration, No metabolism of YM466 was observed in an in vitro liver microsome study. These findings suggest that the low bioavailability of YM466 is attributable to the poor absorption not to the extensive metabolism.
Descriptors: metabolism, pharmacology, drug metabolism, total drug clearance.

Markos, F., B.A. Hennessy, M. Fitzpatrick, J. O'sullivan, and H.M. Snow (2002). **The effect of tezosentan, a non-selective endothelin receptor antagonist, on shear stress-induced changes in arterial diameter of the anaesthetized dog.** *Journal of Physiology* 544(3): 913-918. ISSN: 0022-3751.
NAL Call Number: 447.8 J82
Abstract: The effects of changes in the mean (Sm) and pulsatile (Sp) components of arterial wall shear stress on arterial dilatation of the iliac artery of the anaesthetized dog were examined in the absence and presence of the endothelin receptor antagonist tezosentan (10 mg kg-1 I.V.; Ro 61-0612; (5-isopropyl-pyridine-2-sulphonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide)). Changes in shear stress were brought about by varying local peripheral resistance and stroke volume using a distal infusion of acetylcholine and stimulation of the left ansa subclavia. An increase in Sm from 1.81+-0.3 to 7.29+-0.7 N m-2 (means+-S.E.M.) before tezosentan caused an endothelium-dependent arterial dilatation which was unaffected by administration of tezosentan for a similar increase in Sm from 1.34+-0.6 to 5.76+-1.4 N m-2 (means+-S.E.M.). In contrast, increasing the Sp from 7.1+-0.8 to a maximum of 11.5+-1.1 N m-2 (means+-S.E.M.) before tezosentan reduced arterial diameter significantly. Importantly, after administration of tezosentan subsequent increases in Sp caused arterial dilatation for the same increase in Sp achieved prior to tezosentan, increasing from a baseline of 4.23+-0.4 to a maximum of 9.03+-0.9 N m-2 (means+-S.E.M.; P<0.001). In conclusion, the results of this study provide the first in vivo evidence that pulsatile shear stress is a stimulus for the release of endothelin from the vascular endothelium.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, arterial diameter, arterial dilatation, arterial wall shear stress, pulsatile components, endothelium dependent arterial dilatation, shear stress induced changes, stroke volume.

Marsella, R., C.F. Nicklin, S. Saglio, and J. Lopez (2004). **Investigation on the effects of topical therapy with 0.1% tacrolimus ointment (Protopic) on intradermal skin test reactivity in atopic dogs**. *Veterinary Dermatology.* 15(4): 218-224. ISSN: 0959-4493.

NAL Call Number: SF901.V47

Abstract: Tacrolimus ointment (TAC) is an effective treatment for atopic dermatitis in humans and dogs. The purposes of the present study were to evaluate the effect of 4 weeks of TAC on intradermal skin testing (IST), and in case of suppression, to investigate if reactivity returned to baseline by 2 or 4 weeks post treatment. Intradermal skin test was performed using saline, histamine, lipopolysaccharide (LPS, 0.4 mg mL-1), house dust (25 PNU mL-1) and house dust mite (1:40 000 w/v) at weeks 0, 4, 6 and 8 on nine dogs enrolled in a blinded, crossover, clinical trial, using 0.1% TAC or placebo once daily for 4 weeks. Reactions were evaluated at 15 min, and at 4 and 6 h. Ointment was applied after the 15-min evaluation on weeks 0 and 4. Data were analysed using the statistical software SAS System for Windows. At week 4, TAC did not affect 15-min IST, but some reactions in the TAC group were suppressed at 6 h compared to baseline. In the TAC group, 4-h IST reactivity was reduced 2 weeks after discontinuation but returned to baseline by 4 weeks. In conclusion, TAC has no effect on immediate reactions but decreased some late-phase reactions. Therefore, no withdrawal is recommended to evaluate only immediate reactions, but a 4-week withdrawal may be necessary for evaluation of late-phase reactions.

Descriptors: atopy, dermatitis, dermatological agents, drug therapy, ointments, pharmacology, skin diseases, skin tests, topical application.

Language of Text: , LS=German; Spanish; French.

Mata Bilbao, M.L., C. Andres Lacueva, E. Roura, O. Jauregui, E. Escribano, C. Torre, and R.M. Lamuela Raventos (2008). **Absorption and pharmacokinetics of green tea catechins in beagles.** *British Journal of Nutrition* 100(3): 496-502. ISSN: 0007-1145.

NAL Call Number: 389.8 B773

Abstract: The present study evaluates for the first time in dogs, the kinetics of green tea catechins and their metabolic forms in plasma and urine. Ten beagles were administered 173 mg (12.35 mg/kg body weight) of catechins as a green tea extract, in capsules. Blood samples were collected during 24 h after intake and urine samples were collected during the following periods of time: 0-2, 2-6, 6-8 and 8-24 h. Two catechins with a galloyl moiety and three conjugated metabolites were detected in plasma. Most of the detected forms in plasma reached their maximum plasma concentration (Cmax) at around 1 h. Median Cmax for (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin glucuronide (EGC-glucuronide), (-)-epicatechin glucuronide (EC-glucuronide), (-)-epicatechin sulphate (EC-sulphate) were 0.3 (range 0.1-1.9), 0.1 (range 0-0.4), 0.8 (range 0.2-3.9), 0.2 (range 0.1-1.7) and 1 (range 0.3-3.4) micromol/l, respectively. The areas under the plasma concentration v. time curves (AUC0 --> 24) were 427 (range 102-1185) micromol/l x min for EGC-glucuronide, 112 (range 53-919) micromol/l x min for EC-sulphate, 71 (range 26-306) micromol/l x min for EGCG, 40 (range 12-258) micromol/l x min for EC-glucuronide and 14 (range 0.1-124) micromol/l x min for ECG. The values of mean residence time (MRT0 --> 24) were 5 (range 2-16), 2 (range 1-11), 10 (range 2-13), 3 (range 2-16) and 2.4 (range 1-18) h for EGCG, ECG, EGC-glucuronide, EC-glucuronide and EC-sulphate, respectively. In urine, catechins were present as conjugated forms, suggesting bile excretion of EGCG and ECG. Green tea catechins are absorbed following an oral administration and EGC-glucuronide is the metabolic form that remains in the organism for a longer period of time, suggesting that this compound could suffer an enterohepatic cycle.

Descriptors: antioxidants pharmacokinetics, catechin pharmacokinetics, dogs metabolism, tea, administration, oral, biological availability, biotransformation, catechin analogs and derivatives, catechin analysis, catechin chemistry, catechin metabolism, glucuronides analysis, glucuronides metabolism, intestinal absorption drug effects, models, animal, sulfuric acid esters analysis, sulfuric acid esters metabolism, time factors.

Mata Bilbao, M.L., C. Andres Lacueva, E. Roura, O. Jauregui, E. Escribano, C. Torre, and R.M. Lamuela Raventos (2007). **Absorption and pharmacokinetics of grapefruit flavanones in beagles.** *British Journal of Nutrition* 98(1): 86-92. ISSN: 0007-1145.
NAL Call Number: 389.8 B773
Abstract: The present study evaluated the pharmacokinetics of three different grapefruit flavanone forms in dog plasma and demonstrated their absorption after an oral intake of a grapefruit extract; pharmacokinetic parameters of these forms were also determined. Ten healthy beagles were administered 70 mg citrus flavonoids as a grapefruit extract contained in capsules, while two additional dogs were used as controls and given an excipient. The grapefruit flavanone naringin, along with its metabolites naringenin and naringenin glucuronide, was detected in dog plasma. Blood samples were collected between 0 and 24 h after administration of the extract. Naringin reached its maximun plasma concentration at around 80 min, whereas naringenin and naringenin glucuronide reached their maximun plasma concentrations at around 20 and 30 min, respectively. Maximum plasma concentrations of naringin, naringenin and naringenin glucuronide (medians and ranges) were 0.24 (0.05-2.08), 0.021 (0.001-0.3) and 0.09 (0.034-0.12) micromol/l, respectively. The areas under the curves were 23.16 l (14.04-70.62) min x micromol/for nariningin, 1.78 (0.09-4.95) min x micromol/l for naringenin and 22.5 (2.74-99.23) min x micromol/l for naringenin glucuronide. The median and range values for mean residence time were 3.3 (1.5-9.3), 2.8 (0.8-11.2) and 8.0 (2.3-13.1) h for naringin, naringenin and naringenin glucuronide, respectively. The results of the present study demonstrate the absorption of grapefruit flavanones via the presence of their metabolites in plasma, thus making an important contribution to the field since the biological activities ascribed to these compounds rely on their specific forms of absorption.
Descriptors: citrus paradisi chemistry, flavanones pharmacokinetics, absorption, administration, oral, biological availability, dogs, flavanones administration and dosage, flavanones blood, intestinal absorption, models, animal, plant extracts administration and dosage, plant extracts pharmacokinetics.

Mattiuz, E.L., G.D. Ponsler, R.J. Barbuch, P.G. Wood, J.H. Mullen, R.L. Shugert, Q. Li, W.J. Wheeler, F. Kuo, P.C. Conrad, and J.M. Sauer (2003). **Disposition and metabolic fate of atomoxetine hydrochloride: pharmacokinetics, metabolism, and excretion in the fischer 344 rat and beagle dog.** *Drug Metabolism and Disposition* 31(1): 88-97. ISSN: 0090-9556.
NAL Call Number: RM301.35.D78
Abstract: These studies were designed to characterize the disposition and metabolism of atomoxetine hydrochloride ((-)-N-methyl-gamma-(2-methylphenoxy)benzenepropanamine hydrochloride; formerly know as tomoxetine hydrochloride) in Fischer 344 rats and beagle dogs. Atomoxetine was well absorbed from the gastrointestinal tract and cleared primarily by metabolism with the majority of its metabolites being excreted into the urine, 66% of the total dose in the rat and 48% in the dog. Fecal excretion, 32% of the total dose in the rat and

42% in the dog, appears to be due to biliary elimination and not due to unabsorbed dose. Nearly the entire dose was excreted within 24 h in both species. In the rat, low oral bioavailability was observed (F=4%) compared with the high oral bioavailability in dog (F=74%). These differences appear to be almost purely mediated by the efficient first-pass hepatic clearance of atomoxetine in rat. The biotransformation of atomoxetine was similar in the rat and dog, undergoing aromatic ring hydroxylation, benzylic oxidation (rat only), and N-demethylation. The primary oxidative metabolite of atomoxetine was 4-hydroxyatomoxetine, which was subsequently conjugated forming O-glucuronide and O-sulfate (dog only) metabolites. Although subtle differences were observed in the excretion and biotransformation of atomoxetine in rats and dogs, the primary difference observed between these species was the extent of first-pass metabolism and the degree of systemic exposure to atomoxetine and its metabolites.
Descriptors: metabolism, pharmacology, species differences.

Mc Entee, K., C. Clercx, D. Soyeur, H. Amory, C. Michaux, T. Flandre, E. Jonville, C. Pynnaert, N. Miserque, and M. Henroteaux (2001). **Usefulness of dobutamine stress tests for detection of cardiac abnormalities in dogs with experimentally induced early left ventricular dysfunction**. *American Journal of Veterinary Research* 62(3): 448-455. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Abstract: Objective: To determine whether dobutamine stress tests (DST) can be used to detect cardiac dysfunction in dogs with early left ventricular dysfunction (ELVD) induced by rapid right ventricular pacing (RRVP). Animals: 7 adult male Beagles. Procedure: A pacemaker was surgically implanted in each dog at the level of the right ventricular apex. Electrocardiography, Doppler sphygmomanometry, and Doppler echocardiography were performed before and during a DST prior to activation of the pacemaker and every 3 to 4 days during the period of RRVP. Dobutamine stress tests were performed by infusing dobutamine at incremental dosages ranging from 12.5 to 42.5 mug/kg of body weight/min. Results: Clinical signs of congestive heart failure were not observed during the pacing period. However, all dogs developed ELVD associated with significant changes in values for most Doppler echocardiographic variables obtained prior to DST. Adverse cardiac effects were not detected during DST. Most Doppler echocardiographic indices of cardiac function were significantly altered in response to dobutamine infusion during the pacing period, compared with prepacing values. However, a dobutamine-induced 2-fold increase in cardiac output was maintained. Conclusions and Clinical Relevance: Dobutamine stress tests can be safely performed in dogs with experimentally induced ELVD. Dobutamine stress tests may be a sensitive, noninvasive diagnostic method, complementary to standard clinical examinations, for detection of early cardiac dysfunction in dogs asymptomatic for dilated cardiomyopathy.
Descriptors: veterinary medicine, medical sciences, methods and techniques, pharmacology, cardiovascular system, transport and circulation, cardiac abnormalities, heart disease, dilated cardiomyopathy, left ventricular dysfunction, experimentally induced early disease model, dobutamine stress test, detection method, diagnostic method.

Mcverry, B.J., X. Peng, P.M. Hassoun, S. Sammani, B.A. Simon, and J.G.N. Garcia (2004). **Sphingosine 1-phosphate reduces vascular leak in murine and canine models of acute lung injury**. *American Journal of Respiratory and Critical Care Medicine* 170(9): 987-993. ISSN:

1073-449X.
NAL Call Number: RC705 .A4
Abstract: Excessive mechanical stress is a key component of ventilator-associated lung injury, resulting in profound vascular leak and an intense inflammatory response. To extend our in vitro observations concerning the barrier-protective effects of the lipid growth factor sphingosine 1-phosphate (Sph 1-P), we assessed the ability of Sph 1-P to prevent regional pulmonary edema accumulation in clinically relevant rodent and canine models of acute lung injury induced by combined intrabronchial endotoxin administration and high tidal volume mechanical ventilation. Intravenously delivered Sph 1-P significantly attenuated both alveolar and vascular barrier dysfunction while significantly reducing shunt formation associated with lung injury. Whole lung computed tomographic image analysis demonstrated the capability of Sph 1-P to abrogate significantly the accumulation of extravascular lung water evoked by 6-hour exposure to endotoxin. Axial density profiles and vertical density gradients localized the Sph 1-P response to transitional zones between aerated and consolidated lung regions. Together, these results indicate that Sph 1-P represents a novel therapeutic intervention for the prevention of pulmonary edema related to inflammatory injury and increased vascular permeability.
Descriptors: pharmacology, respiratory system, respiration, lung injury, injury, respiratory system disease, pulmonary edema, respiratory system disease, drug therapy, pathology, prevention and control, mechanical ventilation, clinical techniques, therapeutic and prophylactic techniques, tomography, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, mechanical stress.

Mealey, K.L., S. Greene, R. Bagley, J. Gay, R. Tucker, P. Gavin, K. Schmidt, and F. Nelson (2008). **P-glycoprotein contributes to the blood-brain, but not blood-cerebrospinal fluid, barrier in a spontaneous canine p-glycoprotein knockout model.** *Drug Metabolism and Disposition the Biological Fate of Chemicals* 36(6): 1073-9.
NAL Call Number: RM300.A1D7
Abstract: P-glycoprotein is considered to be a major factor impeding effective drug therapy for many diseases of the central nervous system (CNS). Thus, efforts are being made to gain a better understanding of P-glycoprotein's role in drug distribution to brain parenchyma and cerebrospinal fluid (CSF). The goal of this study was to validate and introduce a novel P-glycoprotein-deficient (ABCB1-1Delta) canine model for studying P-glycoprotein-mediated effects of drug distribution to brain tissue and CSF. CSF concentrations of drug are often used to correlate efficacy of CNS drug therapy as a surrogate for determining drug concentration in brain tissue. A secondary goal of this study was to investigate the validity of using CSF concentrations of P-glycoprotein substrates to predict brain tissue concentrations. Loperamide, an opioid that is excluded from the brain by P-glycoprotein, was used to confirm a P-glycoprotein-null phenotype in the dog model. ABCB1-1Delta dogs experienced CNS depression following loperamide administration, whereas ABCB1 wild-type dogs experienced no CNS depression. In summary, we have validated a novel P-glycoprotein-deficient canine model and have used the model to investigate transport of the P-glycoprotein substrate (99m)Tc-sestamibi at the blood-brain barrier and blood-CSF barrier.
Descriptors: blood brain barrier metabolism, central nervous system depressants pharmacology, loperamide pharmacology, models, animal, p glycoprotein genetics, technetium tc 99m

sestamibi cerebrospinal fluid, brain metabolism, dogs, technetium tc 99m sestamibi pharmacokinetics.

Miao, C.H., B. Sun, H. Jiang, Z.G. Xue, and R. Lindwall (2002). **Pharmacodynamics and pharmacokinetics of inhaled nitric oxide in dogs with septic acute respiratory distress syndrome.** *Acta Pharmacologica Sinica* 23(3): 278-84. ISSN: 1671-4083.
Abstract: AIM: To evaluate pharmacodynamics and pharmacokinetics of inhaled nitric oxide (iNO) in dogs with acute respiratory distress syndrome (ARDS). METHODS: ARDS, induced after iv injection of endotoxin, was evidenced by reduction of paO2/FiO2 from (62.5 +/- 2.8) to (26 +/- 4) kPa and dynamic lung compliance (Cdyn) from (14.8 +/- 0.7) to (8.6 +/- 0.6) mL.kPa-1 . kg-1, increase of dead space (VD/VT) from (0.14 +/- 0.06) to (0.58 +/- 0.05), intrapulmonary shunting (Qs/Qt) from 4.7 % +/- 1.7 % to 39 % +/- 7 %, and pulmonary vascular resistance index (PVRI) from (16 +/- 4) to (51 +/- 8) kPa.s.L-1 . m-2 (all P < 0.05), along with severe intrapulmonary neutrophil recruitment and peripheral neutropenia. The animals were then treated as either a control or an NO group (n = 6 each, iNO 0.4 - 3.2 micromol/L) for another 10 h. RESULTS: More survival was found in NO group (4/6 vs 0/6, P < 0.05). iNO at 0.8, 1.6, and 3.2 micromol/L (20, 40, and 80 ppm) resulted in > 40 % increase of paO2/FiO2 and Cdyn, a reduction of VD/VT to 0.32, Qs/Qt to < 25 %, and PVRI by > 50 % (30.8 kPa . s . L-1 . m-2) compared to the control. Optimal iNO dose was around 0.8 micromol/L as higher methemoglobin (MetHb, > 3 %) was found at higher NO. iNO had no adverse effects on surfactant phospholipids and lung fluid balance, but attenuated expression of tumor necrosis factor alpha,beta2 integrin CD11b, and interleukin-8 mRNA in the lungs by 22 %, 44 %, and 25 %, respectively (P < 0.05). CONCLUSION: Pharmacodynamics of iNO in this model was related to improvement in gas exchange, Cdyn, PVRI, and suppression of proinflammatory cytokine expression in the lungs, and its adverse effect was mainly confined to MetHb at higher NO dose.
Descriptors: pharmacodynamics, pharmacokinetics, inhaled nitric oxide (iNO), acute respiratory distress syndrome, intrapulmonary neutrophil recruitment, peripheral neutropenia, surfactant phospholipids, lung fluid balance.

Mizutani, T., S. Takahashi, S. Kihara, and H. Toyooka (2001). **Repeated administration of protamine does not attenuate circulatory changes caused by protamine reversal of heparin in dogs.** *Journal of Cardiothoracic and Vascular Anesthesia* 15(3): 346-51. ISSN: 1053-0770.
Descriptors: mongrel dogs, nitric oxide, protamine, circulatory changes, haparin, pharmacology.

Morris, T.A., J.J. Marsh, R. Konopka, C.A. Pedersen, and P.G. Chiles (2004). **Improved imaging of deep venous thrombi during anticoagulation using radiolabelled anti-d-dimer antibodies**. *Nuclear Medicine Communications* 25(9): 917-922. ISSN: 0143-3636.
Abstract: Objectives Radiolabelled anti-fibrin antibodies have not yet enabled reliable and practical diagnosis of venous thromboembolism. However, previous unsuccessful clinical trials were performed with anti-fibrin P-chain antibodies that do not optimally bind to thrombi during anticoagulation. The current experiments were performed to determine if radiolabelled anti-D-dimer antibodies more reliably allowed nuclear medicine imaging

of deep venous thrombi during anticoagulation than anti-beta-chain antibodies. Methods Dogs with pre-existing unilateral femoral vein thrombi were anticoagulated with heparin (300 units-kg bolus followed by 90 units.kg-1 .h-1 continuous infusion). They were then allocated to receive one of three 111In labelled antibodies: anti-D-dimer, anti-beta or a non-specific control antibody. Gamma scans of the legs were performed at regular intervals for 24 h. Scans were interpreted in a blinded fashion and the number of gamma counts from the femoral area on the thrombosed side was compared to the contralateral side. Clot/blood isotope density ratios were determined post-mortem. Results Leg thrombi were 100% detectable in the anti-D-dimer group, but only 60% detectable in the anti-beta group. Mean +/- SD relative counts in the thrombosed femoral area was 137 +/- 10% compared to the contralateral side in the anti-D-dimer group, but only 116 20% in the anti-P group. The clot/blood ratio was 24.5 +/- 2.8 in the anti-D-dimer group, but only 7.8 +/- 2.0 in the anti-beta group. Conclusions 111In labelled anti-D-dimer provides superior nuclear medicine images of thrombi during intensive anticoagulation compared to anti-beta. Clinical results with radiolabelled anti-D-dimer may be more promising than those previously observed with other anti-fibrin antibodies. Copyright 2004 Lippincott Williams & Wilkins.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, femoral vein thrombosis, vascular disease, diagnosis, drug therapy, gamma scan, imaging and microscopy techniques, laboratory techniques, indium 111 labelled anti d dimer antibody imaging, clinical techniques, diagnostic techniques .

Mraovic, B., J.G. Krolikowski, P.S. Pagel, D.C. Warltier, and J.R. Kersten (2003). **Role of cyclooxygenase during ischemic and pharmacological preconditioning in dogs -- selected for journal symposium.** *2003 Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, USA; October 11-15, 2003,*
Abstract: Background: Recent evidence suggests that cyclooxygenase (Cox)-2 antagonists may cause deleterious effects in patients with coronary artery disease. Cox-2 mediates the late phase of ischemic preconditioning (IPC) but the role of Cox to modulate early IPC, anesthetic-induced preconditioning (APC), or pharmacological preconditioning (PPC) are unknown1. We tested the hypothesis that Cox-2 is an essential mediator of IPC, APC, and PPC in dogs. Methods: All experimental procedures conformed to the guidelines of the APS and the NIH and were approved by the Institutional Animal Care and Use Committee. Barbiturate-anesthetized dogs (n = 78) were instrumented for measurement of hemodynamics and left anterior descending coronary artery (LAD) occlusion and reperfusion. The roles of Cox antagonists to modulate IPC, APC or PPC were evaluated in dogs randomly assigned to receive oral aspirin 650 mg, celecoxib 200 mg or acetaminophen 500 mg, respectively, at 24, 12 and 2 h before IPC, APC, and PPC, or during control experiments (without preconditioning stimuli) in 13 separate groups. All dogs were subjected to a 60-min LAD occlusion followed by 3 h of reperfusion. IPC was induced with four 5 min periods of LAD occlusion interspersed with 5 min periods of reperfusion. APC was induced with isoflurane 1.0 minimum alveolar concentration for 30 min and discontinued 30 min before occlusion, and PPC was induced with diazoxide 2.5mg/kg i.v. 30 min before LAD occlusion. Myocardial infarct size and transmural coronary collateral blood flow were measured with triphenyltetrazolium chloride staining and radioactive microspheres, respectively. Statistical analysis of data was performed with ANOVA followed by the Student-Newman-Keuls test. Data were

considered statistically significant when P<0.05 (*versus control experiments). Results: No differences in baseline hemodynamics, coronary collateral blood flow or area of the left ventricle at risk for infarction (AAR) were observed between groups. Myocardial infarct size expressed as a percentage of the AAR was 29+-1% (mean+-SEM) in control experiments. In the absence of Cox antagonists IPC, APC and PPC all significantly decreased myocardial infarct size (8.6+-1*, 12+-1*, and 10+-1%*, respectively). Celecoxib alone had no effect on infarct size (26+-2%) but abolished IPC (30+-3), APC (30 +-3) and PPC (27+-4%). Aspirin and acetaminophen alone did not alter the extent of myocardial infarction (23+-3 and 29+-2%, respectively), but these Cox antagonists modestly attenuated APC (18+-1* and 18+-1%*, respectively). Conclusions: The results indicate that Cox 2 is an important mediator of IPC, APC and PPC. This finding is consistant with the observation that prostacyclin enhances KATP channel activation and these channels are known to mediate IPC, APC and PPC. Cox 1 and Cox 3 may play a role during preconditioning, although, attenuation of APC by aspirin and acetamenophen may have occurred through non-selective actions of these drugs to antagonize Cox-2. The role of Cox enzymes as obligatory mediators in protection by diverse preconditioning stimuli may have implications in the clinical use of selective and non-selective Cox antagonists..

Descriptors: cardiovascular system, transport and circulation, cell biology, enzymology, biochemistry and molecular biophysics, pharmacology, coronary artery disease, heart disease, vascular disease, ischemia, myocardial infarction, anesthetic induced preconditioning, laboratory techniques, ischemic preconditioning, pharmacological preconditioning, hemodynamics .

Murray, C., F. Markos, H.M. Snow, T. Corcoran, N. Parfrey, and G.D. Shorten (2003). **Effects of fenoldopam on renal blood flow and its function in a canine model of rhabdomyolysis.** *European Journal of Anaesthesiology* 20(9): 711-718. ISSN: 0265-0215.

Abstract: Background and objective: Our hypothesis was that fenoldopam, a selective DA1 agonist, would protect against rhabdomyolysis-induced renal injury. Methods: We studied the effects of intravenous fenoldopam (0. 1-1.0 mug kg-1 min-1) or saline on renal blood flow and function in 10 anaesthetized Labrador dogs in whom rhabdomyolysis and myoglobinuric acute renal failure had been induced by administration of glycerol 50% (10 mL kg-1) intramuscularly. Haemodynamic measurements including renal blood flow and derived parameters of renal function including creatinine clearance were recorded before and for the 30 min following glycerol injection, and during the 3 h following commencement of each infusion. Serum malondialdehyde concentrations were measured before and 15 min after glycerol intramuscularly, and 30 and 150 min after commencement of the infusion. Results: In the fenoldopam group, creatinine clearance was less than placebo at 1 and 2 h after commencing the infusion (12.7+-11.5 versus 31.3+-9.9 mL min-1, P=0.04; 8.5+-5.3 versus 20.1+-7.4 mL min-1, P=0.03). A 140-fold increase in serum malondialdehyde concentration occurred in one dog (fenoldopam group). Conclusion: Fenoldopam increased the severity of the renal injury in this canine model of myoglobinuric acute renal failure.

Descriptors: muscular system, movement and support, pharmacology, urinary system, chemical coordination and homeostasis, myoglobinuric acute renal failure, urologic disease, renal injury, injury, urologic disease, rhabdomyolysis, muscle disease, hemodynamics, renal blood flow, renal function.

Nagahara, N., Y. Akiyama, K. Higaki, and T. Kimura (2007). **Animal models for predicting potency of oral sustained-release adhesive microspheres in humans.** *International Journal of Pharmaceutics* 331(1): 46-53. ISSN: 0378-5173.

NAL Call Number: RS122.A1I5

Abstract: The sustained-release (SR) adhesive microspheres successfully improved the absorption of furosemide, of which the absorption is limited to the upper small intestine, after oral administration to humans based on the adhesion to the gastric mucosa in our previous study. To develop a new drug using SR-adhesive microspheres, however, some adequate animal models should be needed to predict the potency of the formulation in humans. To find out an adequate animal model, the effect of the SR-adhesive microspheres on furosemide absorption was investigated in rats, dogs and monkeys and the release kinetics of furosemide from SR-adhesive microspheres was also studied. SR-adhesive and SR-non-adhesive microspheres showed very similar characteristics of drug release. The rotation speed did not affect the release kinetics, but higher pH increased the drug release from both microspheres. The absorption of furosemide after SR-adhesive microspheres administration to rats and dogs was significantly higher than that after SR-non-adhesive microspheres administration, which was very similar to the results obtained in humans. On the other hand, in monkeys, SR-adhesive microspheres were not able to improve the absorption of furosemide at all. These findings indicated that rats and dogs were in vivo animal models suitable for predicting the potency of SR-adhesive microspheres in humans.

Descriptors: furosemide chemistry, furosemide pharmacokinetics, intestinal absorption, microspheres, adhesiveness, administration, oral, delayed action preparations, dogs, macaca fascicularis, models, animal, rats, rats, sprague dawley.

Nagasawa, M., T. Ide, M. Suzuki, M. Tsunoda, Y. Akasaka, T. Okazaki, T. Mochizuki, and K. Murakami (2004). **Pharmacological characterization of a human-specific peroxisome proliferater-activated receptor alpha (PPAR alpha) agonist in dogs**. *Biochemical Pharmacology* 67(11): 2057-2069. ISSN: 0006-2952.

NAL Call Number: 396.8 B52

Abstract: Peroxisome proliferator-activated receptor alpha (PPAR alpha) is a key regulator in lipid metabolism and a potential therapeutic target for lipid-related metabolic diseases. It has been shown that there are species differences between human and mouse in response to several PPAR alpha agonists in a transactivation assay. In the present study, we cloned a full length of dog PPAR alpha and investigated the effects of a novel and potent agonist (KCL) for human PPAR alpha . In a transactivation assay using the full length of PPAR alpha , agonistic activity of KCL for dog PPAR alpha (EC50: 0.007 micro M) was comparable to that for human PPAR alpha (EC50: 0.003 micro M), but not that for rat PPAR alpha (EC50: 11.49 micro M). Similar results were obtained from a transactivation assay using a GAL4/PPAR alpha ligand-binding domain (LBD) chimera. A point-mutation study showed that I272 on PPAR alpha LBD is a major contributor to species differences in response to KCL between human, dog, and rat PPAR alpha . KCL also induced mRNA levels of HMG-CoA synthase in dog hepatocytes. When administered orally to dogs and rats, KCL significantly decreased plasma triglyceride levels in a dose-dependent manner. The triglyceride-lowering effects of KCL in dogs were >100-fold more potent than those in rats. These results suggest that KCL may induce activation of highly potent PPAR alpha in humans as well as dogs,

and that dog is a suitable animal model for studying and predicting the biological actions of potent agonists for human PPAR alpha .
Descriptors: animal models, laboratory animals, peroxisomes, pharmacology, potassium chloride, transcription factors, triacylglycerols, dogs, rats, species differences.

Nanri, M., N. Mori, T. Kirimoto, T. Uji, and M. Kiniwa (2004). **The effect of propiverine hydrochloride in a canine urinary frequency model associated with bladder hyperactivity.** *Journal of Pharmacological Sciences* 94(Supplement 1): 265P. ISSN: 1347-8613.
Descriptors: pharmacology, urinary system, chemical coordination and homeostasis, veterinary medicine, medical sciences, bladder hyperactivity, urologic disease, lower urinary tract dysfunction, urologic disease, micturition interval

Narisawa, S., M. Nagata, T. Ito, H. Yoshino, Y. Hirakawa, and K. Noda (1995). **Drug release behavior in gastrointestinal tract of beagle dogs from multiple unit type rate-controlled or time-controlled release preparations coated with insoluble polymer-based film**. *Journal of Controlled Release* 33(2): 253-260. ISSN: 0168-3659.
NAL Call Number: RS201.C64J68
Abstract: Drug release behaviors from two multiple unit types of controlled release systems were observed in the gastrointestinal (GI) tract of beagle dogs. Factors affecting the in vivo drug release are discussed. The in vivo drug release behaviors were directly predicted by measuring the residual amount of drugs in preparations recovered from the GI tract after oral administration. Theophylline (TP) and propranolol hydrochloride (PPL), which have markedly different solubility, were used as model drugs. A rate-controlled release preparation (porous ethylcellulose film-coated beads) and a time-controlled release preparation (SRS; sigmoidal release system) were examined. Although in vivo TP release from the rate-controlled release beads agreed considerably with in vitro release in the early stages, it was reduced by a lack of fluid in the lower region of the GI tract and the lower water-solublity of the drug. On the other hand, PPL release in vivo was in accord with the in vitro release, and the drug was released almost completely from the beads in the GI tract. In the case of PPL-SRS, although the in vivo release rate was slightly lower than that in vitro, sigmoidal drug release was also observed in the GI tract. TP was not released entirely from the SRS or the porous ethylcellulose film-coated beads in the GI tract. In conclusion, with respect to drug release from controlled release preparations coated with insoluble polymer based-film coating, a good in vitro/in vivo correlation was observed in the early stages of drug release, irrespective of drug properties, but solubility of the drugs was found to be an important factor that affected the drug release in the lower site of GI tract of dogs.
Descriptors: biochemistry and molecular biophysics, digestive system, ingestion and assimilation, pharmacology, drug delivery, ethylcellulose film coating, pharmaceuticals, propranolol hydrochloride, theophylline .

Nolan, E.R., M.B. Bailie, and N.B. Olivier (2008). **Effect of autonomic blockade on ventricular repolarization shortening: response to behavioral stimulus in paced dogs.** *Autonomic Neuroscience Basic and Clinical* 140(1-2): 66-71. ISSN: 1566-0702.
Abstract: Autonomic tone has been suggested to be a significant determinant of ventricular repolarization duration with both rate dependent and independent effects. Using the His

bundle-paced dog, a model that eliminates the need for QT correction factors, we explored the rate-independent effects of sympathetic and parasympathetic blockade on ventricular repolarization shortening following an excitatory stimulus. Six male His bundle-paced beagle dogs were paced at 80 bpm and fitted with jackets, surface ECG electrodes, and radiotelemeters. Dogs were given propranolol, atropine methyl nitrate, or the appropriate control in a four-period crossover design. Doses were based on literature reviews and unpublished pharmacokinetic/pharmacodynamic modeling to provide efficacious beta- and parasympathetic blockade throughout the data collection period. Data collection began at 11 am and concluded at 11 am the following day, with event stimuli provided by investigators entering the room at 5 pm and at 7 am the following morning. One minute of ECG data were sampled every 15 min and these means were averaged to generate hourly means for the 24 hour data collection period. Treatment with atropine attenuated RT interval shortening when compared with the vehicle group at both the 5 pm and 7 am stimulus. In contrast, propranolol was not associated with significant effects on RT interval duration at either time point. These results suggest that parasympathetic withdrawal is the primary factor responsible during both awake hours (5 pm) and in the transition from deep sleep to the awake state (7 am) in the facilitation of RT interval shortening following an excitatory stimulus. The attenuation of RT interval shortening following atropine treatment may be a direct effect, or an indirect effect requiring an excited state to become evident. The use of a model that eliminates the need to apply correction factors to repolarization indices helps to clarify the role of the autonomic nervous system on ventricular repolarization.
Descriptors: autonomic nervous system physiology, heart innervation, heart physiology, heart rate physiology, heart ventricles innervation, ventricular function, adrenergic beta antagonists pharmacology, atropine pharmacology, autonomic nervous system drug effects, biological clocks drug effects, biological clocks physiology, bundle of his drug effects, bundle of his physiology, circadian rhythm physiology, dogs, electric stimulation, electrocardiography drug effects, heart rate drug effects, membrane potentials drug effects, membrane potentials physiology, models, animal, muscarinic antagonists pharmacology, pacemaker, artificial, parasympathetic nervous system drug effects, parasympathetic nervous system physiology, propranolol pharmacology, sympathetic nervous system drug effects, sympathetic nervous system physiology, time factors.

O'reilly, J.D., C.J. Charlton, B.H.E. Smith, and E.J. Harper (2000). **Mild sedation causes oxidative stress in domestic dogs**. *FASEB Journal* 14(4): A200. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: pharmacology, toxicology, lipid peroxidation, mild sedation, oxidative stress, meeting abstract.

Olivry, T., J.S. Paps, P. Bizikova, K.M. Murphy, H.A. Jackson, and J. Zebala (2007). **A pilot open trial evaluating the efficacy of low-dose aminopterin in the canine homologue of human atopic dermatitis.** *British Journal of Dermatology* 157(5): 1040-2. ISSN: 0007-0963.
NAL Call Number: RL1.B7
Descriptors: aminopterin therapeutic use, dermatitis, atopic veterinary, dog diseases drug therapy, folic acid antagonists therapeutic use, dermatitis, atopic drug therapy, dogs, models, animal, pilot projects, treatment outcome.

Ollerstam, A., S.A. Visser, G. Duker, T. Forsberg, A.H. Persson, L.B. Nilsson, J.A. Bjorkman, J. Gabrielsson, and A. Al Saffar (2007). **Comparison of the QT interval response during sinus and paced rhythm in conscious and anesthetized beagle dogs.** *Journal of Pharmacological and Toxicological Methods* 56(2): 131-44. ISSN: 1056-8719.

NAL Call Number: QP901.J6

Abstract: INTRODUCTION: The aim of the present study was to compare sensitivity in detecting the drug-induced QT interval prolongation in three dog models: conscious telemetered at sinus rhythm and conscious and anesthetized dogs during atrial pacing. The test substances used represent different chemical classes with different pharmacological and pharmacokinetic profiles. METHOD: Dofetilide and moxifloxacin were tested in all models, whereas cisapride and terfenadine were tested in the conscious telemetered and paced models. All substances were given as two consecutive 1.5-h intravenous infusions (infusions 1 and 2). The individual concentration-time courses of dofetilide, moxifloxacin, and cisapride were linked to the drug-induced effects on the QT interval and described with a pharmacokinetic-pharmacodynamic model to obtain an estimate of the unbound plasma concentrations at steady state that give a 10- and 20-ms drug-induced QT interval prolongation (CE10ms and CE20ms). RESULTS: In the conscious telemetered, conscious paced, and anesthetized dog models, the mean CE10ms values were 1.4, 4.0, and 2.5 nM for dofetilide and 1300, 1800, and 12,200 nM for moxifloxacin. For cisapride, the CE10ms values were 8.0 and 4.4 nM in the conscious telemetered and conscious paced dog models. The drug-induced QT interval prolongation during the last 30 min of infusions 1 and 2 was comparable in the conscious models, but smaller in the anesthetized dog model. Terfenadine displayed a marked delay in onset of response, which could only be detected by the extended ECG recording. DISCUSSION: All dog models investigated detected QT interval prolongation after administration of the investigated test substances with similar sensitivity, except for a lower sensitivity in the anesthetized dogs following moxifloxacin administration. The conscious telemetered dog model was favorable, mainly due to the extended continuous ECG recording, which facilitated detection and quantification of delayed temporal differences between systemic exposure and drug-induced QT interval prolongation.

Descriptors: cardiac pacing, artificial, long qt syndrome physiopathology, sinoatrial node physiopathology, telemetry methods, anesthesia, aza compounds administration and dosage, aza compounds pharmacokinetics, aza compounds toxicity, cisapride administration and dosage, cisapride pharmacokinetics, cisapride toxicity, consciousness, dogs, dose response relationship, drug, drug evaluation, preclinical methods, electrocardiography methods, ether a go go potassium channels physiology, half life, heart rate drug effects, infusions, intravenous, long qt syndrome chemically induced, models, animal, phenethylamines administration and dosage, phenethylamines pharmacokinetics, phenethylamines toxicity, quinolines administration and dosage, quinolines pharmacokinetics, quinolines toxicity, sinoatrial node drug effects, sulfonamides administration and dosage, sulfonamides pharmacokinetics, sulfonamides toxicity, terfenadine administration and dosage, terfenadine pharmacokinetics, terfenadine toxicity, time factors.

Olmos Zuniga, J.R., C. Hernandez Jimenez, E. Diaz Martinez, R. Jasso Victoria, A. Sotres Vega, M.O. Gaxiola Gaxiola, J. Villalba Caloca, M. Baltazares Lipp, P. Santillan Doherty, and J.A. Santibanez Salgado (2007). **Wound healing modulators in a tracheoplasty canine model.**

Journal of Investigative Surgery the Official Journal of the Academy of Surgical Research 20(6): 333-8. ISSN: 0894-1939.

Abstract: Postsurgical tracheal stenosis results from fibrosis formation due to ischemia. There are healing modulators, hyaluronic acid (HA) and collagen polyvinylpyrrolidone (CPVP), which reduce collagen fibers formation. Thus we can hypothesize that the topical application of one of these modulators can diminish postsurgical tracheal scarring and stenosis. The aim of this work was to evaluate the macroscopic, microscopic, and biochemical changes of tracheal healing after the application of HA or CPVP in a canine tracheoplasty model. The study design was prospective experimental investigation in a canine model. Eighteen mongrel dogs underwent three cervical tracheal rings resection and end-to-end anastomosis. They were randomized into three groups according to treatment: group I (control group) (n = 6), topical application of saline solution on tracheal anastomosis; group II (n = 6), topical application of 15 microg HA on tracheal anastomosis; and group III (n = 6), topical application of 2.5 mg CPVP on tracheal anastomosis. They were evaluated clinical, radiological and tracheoscopically during 4 weeks. They were euthanized at the end of the study time. Macroscopic, microscopic, and biochemical changes of tracheal anastomosis healing were analyzed. Collagen formation was quantified by the Woessner method. All the animals survived the surgical procedure and study period. Macroscopic, radiologic, and endoscopic studies showed that animals in group I developed tracheal stenosis, inflammation, and firm fibrous tissue formation, and histological studies also showed severe inflammatory reaction and fibrosis formation. Groups II (HA) and III (CPVP) showed well-organized thin collagen fibers with minimal inflammatory response. Biochemical evaluation revealed a higher collagen concentration in group I animals (analysis of variance [ANOVA] $p < .05$ and Tukey $p < .01$). Thus, hyaluronic acid or collagen polyvinylpyrrolidone administered after tracheal anastomosis diminished the degree of stenosis and inflammatory reaction. Both modulators improved tracheal healing.

Descriptors: collagen pharmacology, hyaluronic acid pharmacology, povidone pharmacology, trachea surgery, wound healing drug effects, dogs, fibrosis, models, animal, postoperative complications etiology, trachea pathology, tracheal stenosis etiology.

Padda, G.S., C. Kishioka, and B.K. Rubin (2001). **Propofol and methohexital have no significant effect on mucus secretion or clearance in the anesthetized dog.** *Critical Care Med.Icine* 29(5): 1045-8. ISSN: 0090-3493.

Abstract: OBJECTIVE: Anecdotal reports suggest that propofol (Diprivan) may stimulate mucus hypersecretion in patients without pulmonary disease. The purpose of this study was to evaluate the effect of methohexital or propofol anesthesia on the physical and transport properties of airway mucus in spontaneously breathing dogs. DESIGN: Randomized, controlled, crossover laboratory study. SETTING: University laboratory. SUBJECTS: Four healthy, purpose-bred female beagle dogs. INTERVENTIONS: Dogs were anesthetized with 5 mg/kg of propofol by intravenous bolus followed by a maintenance infusion at 0.4 mg x kg(-1) x min(-1) or 4 mg/kg of methohexital followed by an infusion at 0.3 mg x kg(-1) x min(-1). Premedication with 0.05 mg/kg of acepromazine was given, and either atropine (0.2 mg) or saline was given by intravenous bolus at the time of induction. Dogs were intubated but spontaneously breathing throughout the experiment. Tracheal secretions were collected after induction and again after 40 mins. MEASUREMENTS AND MAIN RESULTS: The

volume of secretions collected on the endotracheal tube during the 1.5-hr experiment and on a bronchoscopy brush over 10 mins during the experiment was measured. Tracheal epithelial potential difference was measured bronchoscopically by saturated agar bridges, and tracheal mucus transport velocity was determined by timing particle transport. The dynamic viscoelasticity of collected mucus was assessed by microrheometry, and secretion mucociliary transportability was measured in vitro. There were no differences in any physical or transport properties of airway secretions that could be attributed to the anesthetic agent. Secretion volume was significantly lower ($p < .05$) and epithelial potential difference was significantly higher ($p = .03$) with atropine premedication. Despite this, there were no differences in tracheal mucus transport velocity, viscoelasticity, or secretion mucociliary transportability with either anesthetic agent or with atropine. CONCLUSIONS: This study suggests that neither methohexital nor propofol significantly affects mucus secretion or clearance in healthy dogs.
Descriptors: female, beagle dogs, methohexital nor propofol, anesthesia, mucus secretion.

Qian, M., W. West, J.T. Wu, B. Lu, and D.D. Christ (2003). **Development of a dog microdialysis model for determining synovial fluid pharmacokinetics of anti-arthritis compounds exemplified by methotrexate.** *Pharmaceutical Research* 20(4): 605-610. ISSN: 0724-8741.
NAL Call Number: RS1
Abstract: Purpose: The purpose of this study was to develop and validate an animal model of drug disposition in synovial fluid (SF) by comparing microdialysis with arthrocentesis using the anti-arthritic drug methotrexate (MTX). Methods: Microdialysis probes were calibrated in vitro with the no net flux method using dog synovial fluid. The probes were implanted surgically into the stifle joint space of four dogs and were dialyzed overnight using a portable microinfusion pump. The membrane integrity of the probes was monitored by retrodialysis using an internal standard. After an intravenous bolus of 2.5 mg/kg of MTX, unbound concentrations in synovial fluid, as well as total plasma concentrations, were measured by liquid chromatography tandam mass spectrometer (LC/MS/MS) in samples collected from 0 to 48 h postdose. Results: The probe membrane remained intact at least 48 h after implantation. The mean probe recovery and unbound fraction of MTX in SF were 46.8% and 44.8%, respectively. The unbound fraction of MTX was 44% in synovial fluid. MTX penetrated into the joint space rapidly, with maximal concentrations of 6.6 muM reached at approximately 1 h postdose. The unbound MTX area under the curve in SF was approximately 40% of the total area under the curve in plasma. These data agree well with the previous data obtained for MTX using arthrocentesis. Conclusion: In contrast with arthrocentesis, microdialysis enables the collection of multiple serial SF samples from individual animals with minimal trauma and potential blood contamination. This animal model should prove valuable for studying the disposition of new anti-arthritis compounds or biomarkers in SF.
Descriptors: models and simulations, computational biology, pharmacology, skeletal system, movement and support, arthritis, joint disease, liquid chromatography tandem mass spectroscopy, chromatographic techniques, spectrum analysis techniques, no net flux method, retrodialysis, laboratory techniques, dog microdialysis model.

Rees, C.A. and D.M. Boothe (2004). **Evaluation of the effect of cephalexin and enrofloxacin on clinical laboratory measurements of urine glucose in dogs**. *Journal of the American Veterinary Medical Association* 224(9): 1455-1458. ISSN: 0003-1488.

NAL Call Number: 41.8 Am3
Abstract: Objective-To determine the effects of cephalexin and enrofloxacin on results of 4 commercially available urine glucose tests in dogs. Animals-6 healthy adult female dogs. Procedure-In a crossover design, cephalexin (22 and 44 mg/kg (10 and 20 mg/lb), PO, q8h) or enrofloxacin (5 and 10 mg/kg (2.3 and 4.5 mg/lb), PO, q 12 h) was administered to dogs for 1 day. Urine samples were tested for glucose at 0, 6, and 24 hours after drug administration. In vitro, dextrose was added to pooled glucose-negative canine urine samples containing either no antimicrobial or known concentrations of either antimicrobial; urine samples were then tested for glucose. Results-In vivo, false-positive results were obtained by use of a tablet test in the presence of both antimicrobials and by use of a strip test in the presence of cephalexin. In vitro, false-positive results were obtained with the tablet test at the highest urine concentration of cephalexin (2,400 mug/mL) and with a strip test at the highest concentration of enrofloxacin (600 mug/mL). Enrofloxacin in urine samples containing dextrose caused the urine glucose tests to underestimate urine glucose concentration. Conclusions and Clinical Relevance-Cephalexin and enrofloxacin at dosages used in clinical practice may result in false-positive or false-negative urine glucose results, and care should be taken when using urine as a basis for identifying or monitoring diabetic animals.
Descriptors: metabolism, pharmacology, veterinary medicine, medical sciences, diabetes, endocrine disease, pancreas, metabolic disease.

Rigaud, M., P. Filip, P. Lirk, A. Fuchs, G. Gemes, and Q. Hogan (2008). **Guidance of block needle insertion by electrical nerve stimulation: a pilot study of the resulting distribution of injected solution in dogs.** *Anesthesiology* 109(3): 473-8.
Abstract: BACKGROUND: Little is known regarding the final needle tip location when various intensities of nerve stimulation are used to guide block needle insertion. Therefore, in control and hyperglycemic dogs, the authors examined whether lower-intensity stimulation results in injection closer to the sciatic nerve than higher-threshold stimulation. METHODS: During anesthesia, the sciatic nerve was approached with an insulated nerve block needle emitting either 1 mA (high-current group, n = 9) or 0.5 mA (low-current group, n = 9 in control dogs and n = 6 in hyperglycemic dogs). After positioning to obtain a distal motor response, the lowest current producing a response was identified, and ink (0.5 ml) was injected. Frozen sections of the tissue revealed whether the ink was in contact with the epineurium of the nerve, distant to it, or within it. RESULTS: In control dogs, the patterns of distribution using high-threshold (final current 0.99 +/- 0.03 mA, mean +/- SD) and low-threshold (final current 0.33 +/- 0.08 mA) stimulation equally showed ink that was in contact with the epineurium or distant to it. One needle placement in the high-threshold group resulted in intraneural injection. In hyperglycemic dogs, all needle insertions used a low-threshold technique (n = 6, final threshold 0.35 +/- 0.08 mA), and all resulted in intraneural injections. CONCLUSIONS: In normal dogs, current stimulation levels in the range of 0.33-1.0 mA result in needle placement comparably close to the sciatic nerve but do not correlate with distance from the target nerve. In this experimental design, low-threshold electrical stimulation does not offer satisfactory protection against intraneural injection in the presence of hyperglycemia.
Descriptors: coloring agents administration and dosage, electric stimulation methods, hyperglycemia physiopathology, needles, sciatic nerve physiopathology, coloring agents phar-

macokinetics, disease models, animal, dogs, models, animal, peripheral nerves physiology, peripheral nerves physiopathology, pilot projects, random allocation, sciatic nerve physiology.

Riou, L.M., C. Ghezzi, G. Vanzetto, A. Broisat, J.P. Mathieu, R. Bontron, R. Pasqualini, and D. Fagret (2003). **Verapamil does not inhibit 99mtcn-noet uptake in situ in normal or ischemic canine myocardium.** *Journal of Nuclear Medicine* 44(6): 981-987. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Abstract: Bis(N-ethoxy,N-ethyldithiocarbamato)nitrido technetium (V) (99mTc) (99mTcN-NOET) is a new myocardial perfusion imaging agent currently undergoing phase III clinical trials in the United States and in Europe. 99mTcN-NOET cellular uptake has been shown to be inhibited by the calcium channel inhibitor verapamil in cultured newborn rat cardiomyocytes. However, the effect of verapamil on in situ 99mTcN-NOET myocardial uptake remains unknown. Therefore, the aim of this study was to evaluate whether the inhibitory effect of verapamil on the cellular uptake of 99mTcN-NOET shown in vitro could be reproduced in situ in a canine model of normal and ischemic myocardium. Methods: 99mTcN-NOET uptake in normal and ischemic myocardium (70% flow reduction in the left anterior descending coronary artery) was measured in the absence or presence of verapamil (0.015 mg/kg/minX10 min) in anesthetized, open-chest dogs (n=17). Control animals were infused with adenosine (0.2 mg/kg/min) to match the verapamil-induced increase in flow. Results: By verapamil treatment, a clinically relevant plasma concentration of the calcium channel inhibitor was attained (mean+-SEM, 290+-152 ng/mL). In normal myocardium (n=8), regional blood flow at the time of 99mTcN-NOET injection was not statistically different in verapamil- and adenosine-treated dogs (1.69+-0.03 vs. 1.61+-0.04 mL/min/g, respectively). 99mTcN-NOET uptake was slightly higher in the presence of verapamil (0.39+-0.01 vs. 0.38+-0.01 counts per minute (cpm)/(Bq/kg)/g for adenosine; P=0.04). However, no significant difference in 99mTcN-NOET myocardial uptake was observed after normalization of the tracer uptake to regional myocardial blood flow. In ischemic myocardium (n=9), regional blood flow was lower in verapamil-treated than in adenosine-treated animals (0.22+-0.02 vs. 0.29+-0.03 mL/min/g; P<0.05). 99mTcN-NOET uptake in the ischemic area was not inhibited by verapamil (0.09+-0.01 vs. 0.10+-0.01 cpm/(Bq/kg)/g; P=not significant). Conclusion: Verapamil does not inhibit 99mTcN-NOET uptake in situ in normal and ischemic canine myocardium. These results suggest that verapamil should not affect 99mTcN-NOET myocardial uptake in patients referred for myocardial perfusion imaging.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, radiation biology, myocardial ischemia, heart disease, vascular disease.

Rudmann, D.G., M.E. Mcnerney, S.L. Vandereide, J.K. Schemmer, R.R. Eversole, and S.L. Vonderfecht (2004). **Epididymal and systemic phospholipidosis in rats and dogs treated with the dopamine d3 selective antagonist pnu-177864**. *Toxicologic Pathology* 32(3): 326-332. ISSN: 0192-6233.
Abstract: Repeat dose oral toxicity studies were conducted in rat and dog to assess the safety for human clinical testing of the potent dopamine D3 receptor antagonist, PNU-177864. Systemic phospholipidosis was the principal treatment-related change with epididymal epithelial cell phospholipidosis being the most prominent finding in rats and dogs. Epididymal

epithelial cells had no histologic evidence of degeneration; sperm density and morphology were normal histologically in both species; and sperm concentration, morphology, and motility in the dog were comparable to dogs given vehicle. Other sites with phospholipidosis included lymphoid tissues (lymph nodes, Peyer's patches, and/or spleen), pulmonary alveolar macrophages, and peripheral blood lymphocytes in rats and dogs and adrenal cortex, liver, pituitary, hair follicles, bone marrow lymphocytes and plasma cells, and skeletal muscle in rats only. The phospholipidosis was resolved after a 6-week recovery period in all tissues but epididymis. There was no evidence of cell injury in tissues that had phospholipid accumulations except in rat skeletal muscle that had multifocal myofiber degeneration and necrosis. For clinical trials, serum AST and CK and peripheral blood lymphocyte vacuolation were considered potential safety biomarkers for skeletal muscle degeneration and phospholipidosis, respectively.

Descriptors: metabolism, pharmacology, reproductive system, male, reproduction, toxicology, epididymal phospholipidosis, metabolic disease, rsystemic phospholipidosis, metabolic disease, repeat dose oral toxicity.

Satoh, Y., A. Sugiyama, A. Takahara, K. Chiba, and K. Hashimoto (2004). **Electropharmacological and proarrhythmic effects of a class iii antiarrhythmic drug nifekalant hydrochloride assessed using the in vivo canine models**. *Journal of Cardiovascular Pharmacology* 43(5): 715-723. ISSN: 0160-2446.

Abstract: Cardiovascular effects of Nifekalant were examined using halothane-anesthetized dogs, and its proarrhythmic potential was estimated with chronic complete atrioventricular block dogs. Nifekalant was intravenously administered to the halothane-anesthetized dogs in three doses of 0.03, 0.3, and 3 mg/kg/ 10 minutes with a pause of 20 minutes (n = 6). The low dose hardly affected any of the cardiovascular parameters. The middle dose, a clinically recommended antiarrhythmic dose, decreased the total peripheral resistance, increased the cardiac output, and prolonged the ventricular repolarization phase and effective refractory period. The high dose increased the left ventricular contraction, transiently decreased the mean blood pressure, and enhanced the atrioventricular conduction, besides potentiation of the changes induced by the middle dose. Increment in the repolarization phase by the high dose was greater than that in the refractoriness, leading to increase of ventricular electrical vulnerability. To the atrioventricular block animals, clinically relevant antiarrhythmic dose of 3 mg/kg p.o. of Nifekalant and its 10-times-higher dose were administered. The high dose prolonged QT interval leading to torsades de pointes in all animals (n = 5), which was not detected by the clinical dose (n = 5). These results suggest that antiarrhythmic dose of Nifekalant can be used safely; however, caution should be paid for patients complicating bradycardia and/or a risk of elevated plasma drug concentration.

Descriptors: cardiovascular system, transport and circulation, pharmacology, torsades de pointes, heart disease, atrioventricular conduction, cardiac output, chronic complete atrioventricular block, effective refractory period, left ventricular contraction, mean blood pressure, monophasic action potential, prolonged qt interval, refractoriness, total peripheral resistance, ventricular electrical vulnerability, ventricular repolarization phase.

Satoh, Y., A. Sugiyama, K. Wada, H. Nomura, and K. Hashimoto (2004). **In vivo electropharmacological effects of a class iii antiarrhythmic drug dl-sotalol assessed using halothane anesthetized canine model.** *77th Annual Meeting of the Japanese Pharmacological Society, Osaka, Japan; March 08-10, 2004,*Vol. 94(Supplement 1): 265P,
Descriptors: cardiovascular system, transport and circulation, pharmacology, veterinary medicine, medical sciences, hypotension, vascular disease, blood pressure, left ventricular contraction, ventricular repolarization.

Sattler-J , Hesterberg-R , Lorenz-W , Schmidt-U , Crombach-M , and Stahlknecht-C-D (1985). **Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit relevance for clinical side effects.** *Agents and Actions* 16(3-4): 91-94. ISSN: 0065-4299.
Descriptors: enzymology, biochemistry and molecular biophysics, metabolism , pharmacology, toxicology, neuromuscular blocking drugs, cephalosporins, histamine levels.

Scherkl, R., A. Hashem, and H.H. Frey (1996). **The tissue cage in dogs - a pharmacological model for plasma- and tissue-kinetics [Die gewebekammer ("tissue cage") beim hund - ein pharmakologisches modell zur darstellung von plasma- und gewebekinetik**. *Deutsche Tierarztliche Wochenschrift* 103(5): 174-177. ISSN: 0341-6593.
NAL Call Number: 41.8 B45
Abstract: The tissue kinetics of naproxen, a drug with a long elimination half life was compared with phenylbutazone and flunixin, which have short elimination half lives in dogs following oral administration. Tissue fluid was obtained using "tissue cages" implanted laterally in the neck. An inflammatory response was produced by injecting 1 to 2 ml of 2% carrageenan into the chamber. Drug concentrations were determined throughout the experiments in both plasma and tissue fluid. Naproxen had an elimination half life of about 72 h and remained in similar concentrations in both tissue fluid and plasma. Phenylbutazone had a longer half life in tissue fluid than in plasma. Flunixin concentrations in plasma and exudate attained equilibrium after 2 to 5 h. Afterwards, flunixin became more concentrated in inflammatory exudate exceeding the concentration in plasma by 2 to 10 times, but then declined with an almost identical half-life in both. The number of leukocytes in exudate (used as a measure of inflammation) was reduced for 2 days after phenylbutazone, for 3 to 4 days after flunixin and for 5 to 7 days after administration of naproxen. It is concluded that phenylbutazone and flunixin, and possibly other non-steroidal anti-inflammatory drugs, could be used at lower concentrations than has been calculated using the dynamics of their plasma concentrations.
Descriptors: blood plasma, leukocytes, dosage, drug therapy, phenylbutazone, pharmacokinetics, flunixin, antiinflammatory agents, dogs.
Language of Text: German, LS=.

Schwarte, L.A., O. Picker, S.R. Bornstein, A. Fournell, and T.W. Scheeren (2005). **Levosimendan is superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation in dogs.** *Critical Care Medicine.* 33(1): 135-42. ISSN: 0090-3493.
Abstract: OBJECTIVE: The effect of levosimendan, a novel inotropic vasodilator (inodilator), on the microvascular gastric mucosal hemoglobin oxygenation (muHbo(2)) is unknown. A possible effect could thereby be selective for the splanchnic region or could

primarily reflect changes in systemic oxygen transport (Do(2)) and/or oxygen consumption (Vo(2). We compared systemic and regional effects of levosimendan with those of established inotropes, milrinone and dobutamine. DESIGN: Laboratory experiment. SETTING: University animal research laboratory of experimental anesthesiology. SUBJECTS: Chronically instrumented dogs with flow probes for cardiac output measurement. INTERVENTIONS: Anesthetized, mechanically ventilated dogs (each group n = 6) on different days randomly received levosimendan (10 microg.kg, followed by four infusion steps: 0.125-1.0 microg. kg.min), milrinone (5.0 microg.kg, followed by 1.25-10 microg.kg.min), or dobutamine (2.5-10.0 microg.kg.min). Since these drugs may modify regional or systemic responses to fluid load, an additional predefined volume challenge was subsequently performed with hydroxyethyl starch 6% (10 mL.kg). MEASUREMENTS AND MAIN RESULTS: We measured muHbo(2) (reflectance spectrophotometry), Do(2), Vo(2), and systemic hemodynamics. Levosimendan significantly increased muHbo(2) from baseline (approximately 55% for all groups) to 64 +/- 4% and further to 69 +/- 2% with volume challenge (mean +/- sem). At the systemic level, levosimendan alone only slightly increased Do(2) at a Vo(2). Milrinone elicited similar systemic effects (Do(2), Vo(2), hemodynamics) but failed to increase muHbo(2). Dobutamine, conversely, increased muHbo(2) to a similar extent as levosimendan; however, this was accompanied by marked increases in Do(2) and Vo(2). The gastric mucosa selectivity of these interventions, expressed as slope of the muHbo(2)/Do2 relation, was highest for levosimendan (+1.89 and +1.14, without and with volume challenge), compared with milrinone (+0.45 and + 0.47) and dobutamine (+0.48 and + 0.33). CONCLUSIONS: Levosimendan is superior to milrinone (no significant regional effects) and dobutamine (marked systemic effects) in increasing gastric mucosal oxygenation selectively (i.e., at only moderately increased Do(2) and stable Vo(2). If our experimental data apply to the clinical setting, levosimendan may serve as an option to selectively increase gastrointestinal mucosa oxygenation in patients at risk to develop splanchnic ischemia.
Descriptors: levosimendan, vasodilator, inodilator, gastric mucosal oxygenation, hemodynamics, pharmacology.

Schwartz, L.M., R.B. Jennings, and K.A. Reimer (1995). **Minimum ischemic stress required for myocardial preconditioning in dogs: effect of analgesia, using the opiate agonist-antagonist, butorphanol.** *FASEB Journal* 9(3): A299. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, pharmacology, meeting abstract, pentobarbital .

Shibayama, T., T. Hirota, H. Seki, and S. Kuwahara (2003). **Disposition of the pivaloyloxymethyl (pom) moiety in cs-834, a novel oral carbapenem, in rats and dogs.** *43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA; September 14-17, 2003,*Vol. 43: 232,
Abstract: Background: CS-834 (CS) is an ester-type prodrug of a carbapenem for oral administration. It is important to investigate the metabolic fate of the ester moiety after dosing from the viewpoint of safety. Methods: The metabolism, excretion and tissue distribution of the POM moiety in CS were examined in rats and dogs after single oral administration of CS labeled on the POM moiety, (pivaloyl-14C)CS, at a dose of 12.65

mg/kg. Results: After oral dosing of (pivaloyl-14C)CS, most of the radioactivity in plasma consisted of pivalic acid (PA) and its conjugates, pivaloylglycine (Pgly), pivaloylglucuronide (Pglu) and pivaloylcarnitine (Pcar), in both rats and dogs. The major radioactivities were PA (32% of total radioactivity), Pgly (21%) and Pglu (15%) in rats and PA (27%) and Pglu (43%) in dogs. Recoveries of the radioactivity in the urine and feces within the first day post-dosing were 93.1% and 2.2%, respectively, in rats and 79.3% and 7.6%, respectively, in dogs. In the urine, the conjugates of PA were mainly detected. Pgly, Pglu, Pcar and PA accounted for 45.6, 42.4, 10.2 and 0.9%, respectively, of the dosed radioactivity in rats and 19.6, 60.6, 17.1 and 0.4%, respectively, of the dosed radioactivity in dogs. In most of the tissue, the levels of radioactivity reached the maximum at 1 hr after oral administration to rats. At this time point, the levels of radioactivity in the liver, kidney, Harderian gland, urinary bladder, stomach and small intestine were 3.19-1.46 times higher than that in the plasma, and those in the other tissues were lower. The levels in most of the tissues decreased in parallel with that in plasma. Conclusions: After oral dosing of (pivaloyl-14C)CS, the PA moiety, which is a part of the POM, was metabolized to its conjugate followed by excretion into the urine. This disposition almost is very similar to those of the POM moiety in cephems such as cefditoren pivoxil and cefetamet pivoxil.
Descriptors: infection, pharmacology, bacterial infections, bacterial disease, drug therapy, antibacterial therapy, clinical techniques, therapeutic and prophylactic techniques, chemotherapy , clinical techniques, drug metabolism studies, drug safety, therapeutics .

Shipe, W.D., J.C. Barrow, Z.Q. Yang, C.W. Lindsley, F.V. Yang, K.A. Schlegel, Y. Shu, K.E. Rittle, M.G. Bock, G.D. Hartman, C. Tang, J.E. Ballard, Y. Kuo, E.D. Adarayan, T. Prueksaritanont, M.M. Zrada, V.N. Uebele, C.E. Nuss, T.M. Connolly, S.M. Doran, S.V. Fox, R.L. Kraus, M.J. Marino, V.K. Graufelds, H.M. Vargas, P.B. Bunting, M. Hasbun Manning, R.M. Evans, K.S. Koblan, and J.J. Renger (2008). **Design, synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist.** *Journal of Medicinal Chemistry* 51(13): 3692-5.
NAL Call Number: RS403.A1J6
Abstract: The novel T-type antagonist (S)- 5 has been prepared and evaluated in in vitro and in vivo assays for T-type calcium ion channel activity. Structural modification of the piperidine leads 1 and 2 afforded the fluorinated piperidine (S)- 5, a potent and selective antagonist that displayed in vivo CNS efficacy without adverse cardiovascular effects.
Descriptors: calcium channel blockers chemical synthesis, calcium channel blockers pharmacology, calcium channels, t type metabolism, drug design, piperidines chemical synthesis, piperidines pharmacology, pyrans chemical synthesis, pyrans pharmacology, blood pressure drug effects, calcium channel blockers chemistry, dogs, dose response relationship, drug, haplorhini, heart rate drug effects, models, animal, molecular structure, piperidines chemistry, pyrans chemistry, rats, structure activity relationship.

Silva, F.C., E. Hatschbach, A.F. Lima, Y.K. Carvalho, and F. Massone (2007). **Continuous infusion in adult females dogs submitted to ovariohysterectomy with midazolam-xylazine and/or medetomidine pre-treated with methotrimeprazine and buprenorphine.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(4): 272-8. ISSN: 0102-8650.

Abstract: PURPOSE: To compare, by continuous infusion of ketamine or medetomidine combined to methotrimeprazine and buprenorphine, ketamine and midazolam, the degree of hypnosis, myorelaxation, anesthetic quality and surgical feasibility through evaluation of possible parametric alterations and recovery quality. METHODS: 20 healthy adult females dogs, aged 3 to 5 years, body weight between 7 and 15 kg, were assigned randomly and homogenously to 2 groups of 10 animals each (n=10), group 1 (G1) and group 2 (G2), respectively. Animals of G1 were subjected to a pre-treatment with intravenous 1.0 mg/kg methotrimeprazine and or 3i/kg. After 15 minutes, a 5.0 mg/kg ketamine and 0.2 mg/kg midazolam were intravenously injected. Immediately after induction, an anesthetic combination of 0.4 mg/kg/h midazolam, 20 mg/kg/h ketamine and 1.0 mg/kg/h xylazine, was continuously and intravenously administered for 30 minutes. The same techniques were used in G2 except for the substitution of xylazine for 30ig/kg/h medetomidine. RESULTS: In G1 there was a 1st and 2nd degree atrioventricular heart block, a longer recovery period and lower quality. In G2 a 1st degree atrioventricular heart block occurred but isolated and ephemeral. CONCLUSIONS: The continuous infusion method, besides reducing drugs utilization, prevented collateral effects allowing a more tranquil recovery with no excitations, both protocols permitted the surgical procedure (ovary-hysterectomy) bringing about a reduction in hypnosis and an accentuated myorelaxation. Xylazine and medetomidine showed a similar pharmacodynamic behavior but with different clinical aspects. The electrocardiographic alterations observed in G2 and in a lower degree in G1 must be well studied. Describers: dogs, ketamine, methotrimeprazine, medetomidine, midazolam and xylazine.
Descriptors: adrenergic alpha agonists administration and dosage, anesthetics, intravenous administration and dosage, hypnotics and sedatives administration and dosage, hysterectomy methods, ovariectomy methods, analgesics, opioid administration and dosage, anesthetics, combined administration and dosage, buprenorphine administration and dosage, dogs, dopamine antagonists administration and dosage, drug evaluation, preclinical, hysterectomy standards, infusion pumps, medetomidine administration and dosage, methotrimeprazine administration and dosage, midazolam administration and dosage, models, animal, ovariectomy standards, random allocation, xylazine administration and dosage.

Siwak, C., H. Callahan, P. Gruet, M. Takagi, and N.W. Milgram (1998). **Adrafinil: a novel compound with both behavioral activating and cognitive enhancing effects in aged dogs**. *Society for Neuroscience Abstracts* 24(1-2): 686. ISSN: 0190-5295.
NAL Call Number: QP351.S6
Descriptors: behavior, pharmacology, behavior, learning, meeting abstract, meeting poster

Siwak, C.T., P. Gruet, F. Woehrle, B.A. Muggenburg, H.L. Murphey, and N.W. Milgram (2000). **Comparison of the effects of adrafinil, propentofylline, and nicergoline on behavior in aged dogs.** *American Journal of Veterinary Research* 61(11): 1410-1414. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Descriptors: dogs, age differences, animal behavior, efficacy, mental disorders, drug therapy, quality of life, movement, dosage, pharmacodynamics.
Notes: Includes references.

Stambler, B.S., G. Fenelon, R.K. Shepard, H.F. Clemo, and C.M. Guiraudon (2003). **Characterization of sustained atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure.** *Journal of Cardiovascular Electrophysiology* 14(5): 499-507. ISSN: 1045-3873.
Abstract: Atrial Tachycardia in Heart Failure. Introduction: Atrial arrhythmias often complicate congestive heart failure (CHF). We characterized inducible atrial tachyarrhythmias and electrophysiologic alterations in dogs with CHF and atrial enlargement produced by rapid ventricular pacing. Methods and Results: Endocardial pacing leads were implanted in the right ventricle, right atrium, and coronary sinus in 18 dogs. The right ventricular lead was connected to an implanted pacemaker capable of rapid ventricular pacing. The atrial leads were used to perform electrophysiologic studies in conscious animals at baseline in all dogs, during CHF induced by rapid ventricular pacing at 235 beats/min in 15 dogs, and during recovery from CHF in 6 dogs. After 20 +- 7 days of rapid ventricular pacing, inducibility of sustained atrial tachycardia (cycle length 120 +- 12 msec) was enhanced in dogs with CHF. Atrial tachycardia required a critical decrease in atrial burst pacing cycle length (ltoreq 130 msec) for induction and often could be terminated by overdrive pacing. Calcium antagonists (verapamil, flunarizine, ryanodine) terminated atrial tachycardia and suppressed inducibility. Effective refractory periods at 400- and 300-msec cycle lengths in the right atrium and coronary sinus were prolonged in dogs with CHF. Atrial cells from dogs with CHF had prolonged action potential durations and reduced resting potentials and delayed afterdepolarizations (DADs). Mitochondria from atrial tissue from dogs with CHF were enlarged and had internal cristae disorganization. Conclusions: CHF promotes inducibility of sustained atrial tachycardia. Based on the mode of tachycardia induction, responses to pacing and calcium antagonists, and presence of DADs, atrial tachycardia in this CHF model has a mechanism most consistent with DAD-induced triggered activity resulting from intracellular calcium overload.
Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, arrhythmia, heart disease, atrial tachycardia, congestive heart failure, rapid ventricular pacing.

Stonerook, M., C. Hassler, P. Tosca, J. Merrill, D. Vasconcelos, and A. Smith (2003). **Cardiotoxicity study of nsc-638850 (ucn-01) and cytostar (ara-c) given alone or in combination to beagle dogs.** *Toxicological Sciences* 72(S-1): 36 ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Descriptors: pharmacology, toxicology, cardiotoxicity, heart disease, toxicity, drug induced, ecg, electrocardiography, clinical techniques, diagnostic techniques, cardiovascular evaluation, combination chemotherapy, therapeutic and prophylactic techniques, blood pressure, body temperature, heart rate, necrosis, vascular resistance, venodilation .

Stump, D.G., J.F. Holson, L.B. Pearce, V.T. Rentko, and M.S. Gawryl (2003). **Finding of developmental toxicity studies of hboc-201 in rodent and canine models.** *Birth Defects Research* 68(3): 250. ISSN: 1542-0752.
NAL Call Number: QL991 .T4
Descriptors: development, pharmacology, toxicology .

Sugiyama, A., Y. Satoh, K. Wada, H. Nomura, Y. Nakamura, and K. Hashimoto (2004). **Torsadogenic action of qt-prolonging drugs, astemizole and haloperidol, assessed by the canine chronic atrioventricular block model.** *Journal of Pharmacological Sciences* 94(Supplement 1): 151P. ISSN: 1347-8613.

Descriptors: cardiovascular system, transport and circulation, pharmacology, torsades de pointes, heart disease, toxicity, drug induced, pathology, ventricular fibrillation, holter ecg monitoring, holter electrocardiography monitoring, clinical techniques, intravenous administration, oral administration, clinical techniques, chronic atrioventricular block, effective refractory period, idioventricular automaticity, ventricular repolarization phase

Sumner, D.R., T.M. Turner, R.M. Urban, T. Turek, H. Seeherman, and J.M. Wozney (2004). **Locally delivered rhbmp-2 enhances bone ingrowth and gap healing in a canine model.** *Journal of Orthopaedic Research* 22(1): 58-65. ISSN: 0736-0266.

Abstract: The purpose of the present study was to determine if recombinant human bone morphogenetic protein-2 (rhBMP-2) enhances bone ingrowth into porous-coated implants and gap healing around the implants. In the presence of a 3-mm gap between the implant and host bone, porous-coated implants were placed bilaterally for four weeks in the proximal humeri of skeletally mature, adult male dogs. In three treatment groups, the test implant was treated with HA/TCP and rhBMP-2 in buffer at a dose of 100 mug/implant (n=5), 400 mug/implant (n=6), or 800 mug/implant (n=5) and placed in the left humerus. In these same animals, an internal control implant was treated only with HA/TCP and buffer and placed in the right humerus. These groups were compared with a previously reported external control group of seven animals in which no growth factor was delivered (J. Orthop. Res. 19 (2001) 85). The BMP treated implants in the two lower dose groups had significantly more bone ingrowth than the external controls with the greatest effect in the 100 g/implant group (a 3.5-fold increase over the external control, p=0.008). All three dose groups had significantly more bone formation in the 3-mm gap surrounding the BMP treated implants than the external controls with the greatest effect in the 800 mug group (2.9-fold increase, p<0.001). Thus, application of rhBMP-2 to a porous-coated implant stimulated local bone ingrowth and gap healing. The enhancement of bone formation within the implant (bone ingrowth) was inversely related to dose.

Descriptors: pharmacology, skeletal system, movement and support, bone ingrowth, gap healing.

Takeda, H., A. Matsuzawa, Y. Igawa, Y. Yamazaki, K. Kaidoh, S. Akahane, M. Kojima, H. Miyata, M. Akahane, and O. Nishizawa (2003). **Functional characterization of beta-adrenoceptor subtypes in the canine and rat lower urinary tract.** *Journal of Urology* 170(2 Part 1): 654-658. ISSN: 0022-5347.

NAL Call Number: 448.8 J8234

Abstract: Purpose: We compared the effect of a beta3-adrenoceptor (AR) agonist with that of beta1 and beta2-AR agonists on the urethra and bladder in the dog and rat. Materials and Methods: In an in vitro experiment we studied the relaxant effect of subtype selective beta-AR agonists in canine and rat urethral and bladder smooth muscle using an organ bath method. In addition, in urethane anesthetized rats we measured urethral pressure and bladder pressure simultaneously in the presence of the beta3-agonist CL316243 and the beta2-

agonist procaterol in 4 or 5 animals. Results: In the dog the relaxing effects of isoprenaline in the distal urethra were about half those seen in the detrusor and trigone. The rank order of relaxing potency was CL316243 > dobutamine (beta1-agonist) = procaterol in detrusor and trigone but procaterol > dobutamine = CL316243 in the prostatic and distal urethra. In rat urethral smooth muscle in vitro the corresponding order was procaterol > CL316243 > dobutamine and the maximal relaxation to each agonist was about half that seen in the bladder. In the anesthetized rat procaterol clearly decreased urethral pressure but CL316243 produced only a slight decrease at its maximal dose, although each agonists clearly reduced bladder pressure. The beta2-antagonist ICI-118551 counteracted the decrease in urethral and bladder pressure induced by procaterol. Conclusions: In rats and dogs a selective beta3-AR agonist can decrease bladder pressure without affecting urethral pressure.
Descriptors: biochemistry and molecular biophysics, pharmaceuticals, pharmacology, urinary system, chemical coordination and homeostasis.

Takehana, K., G.A. Beller, M. Ruiz, F.D. Petruzella, D.D. Watson, and D.K. Glover (2001). **Assessment of residual coronary stenoses using 99mtc-n-noet vasodilator stress imaging to evaluate coronary flow reserve early after coronary reperfusion in a canine model of subendocardial infarction**. *Journal of Nuclear Medicine* 42(9): 1388-1394. ISSN: 0161-5505.
NAL Call Number: RM845.J78
Abstract: Reperfusion is often incomplete after recanalization therapy because of the presence of residual coronary stenoses. Detecting mild to moderate stenoses requires assessing coronary flow reserve with vasodilator stress. 99mTc-(N-ethoxy-N-ethyl-dithiocarbamato) nitrido (N-NOET) is a viability-independent flow tracer and thus may be well suited for assessing coronary flow reserve in the acute phase of reperfusion. Methods: Twelve open-chest dogs underwent 60 min of total left anterior descending artery (LAD) occlusion followed by either full reperfusion (group 1; n = 4) or reperfusion through a residual critical stenosis (group 2; n = 8). 99mTc-N-NOET was given during peak vasodilator stress 165 min after reperfusion, and initial and 60-min delayed images were acquired. Regional blood flow was assessed with radiolabeled microspheres. Results: Infarct size was similar in both groups (9% +- 2% vs. 8% +- 2% of left ventricle). Both initial (0.61 +- 0.02 vs. 0.73 +- 0.01; P < 0.01) and 60-min (0.67 +- 0.02 vs. 0.80 +- 0.01; P < 0.01) defect count ratios (LAD/left circumflex coronary artery (LCx)) differentiated between the 2 groups, reflecting the greater diminution in coronary flow reserve in group 2 dogs (LAD/LCx flow ratios = 0.37 +- 0.04 vs. 0.57 +- 0.09; P < 0.01). Interestingly, coronary flow reserve in the reperfused zone of group 1 was diminished despite the absence of a stenosis. Thus, the difference in 99mTc-N-NOET uptake between the 2 groups was less than expected. Conclusion: In this canine myocardial infarction model with some coronary flow reserve preservation, 99mTc-N-NOET imaging can detect residual coronary stenoses. However, with more prolonged occlusion resulting in more severe endothelial or microvascular dysfunction, it may be difficult to distinguish varying degrees of vessel patency using any coronary flow reserve technique.
Descriptors: cardiovascular system, transport and circulation, pharmaceuticals, pharmacology, radiation biology, subendocardial infarction, heart disease, vascular disease, coronary flow reserve, coronary reperfusion, coronary stenosis, nuclear medicine.

Teo, S.K., D.I. Stirling, S.D. Thomas, M.G. Evans, and V.D. Khetani (2003). **A 90-day oral gavage toxicity study of d-methylphenidate and d,l-methylphenidate in beagle dogs.** *International Journal of Toxicology* 22(3): 215-226. ISSN: 1091-5818.

NAL Call Number: RA1190.J61

Abstract: d-Methylphenidate (d-MPH) was approved as a treatment for attention deficit hyperactivity disorder (ADHD) in children. The repeated-dose toxicity of the d enantiomer of d,l-methylphenidate (d,l-MPH) was assessed in male and female Beagle dogs. Dogs were orally dosed twice a day in equally divided doses 6 hours apart for total daily doses of 1, 3, and 10 mg/kg/day d-MPH or 20 mg/kg/day d,l-MPH for 90 days, followed by a 30-day recovery period. The top d-MPH dose of 10 mg/kg was equimolar to 20 mg/kg d,l-MPH in d-MPH content. The 10-mg/kg d-MPH and d,l-MPH doses were at least 13 times the maximum therapeutic dose giving rise to systemic exposures that were equivalent to or at least 2 times greater than those at the maximum therapeutic doses in children. The 10-mg/kg d-MPH and 20-mg/kg d,l-MPH doses had systemic exposures that were equivalent to or two to five times greater than the maximum therapeutic plasma levels in children respectively. There was no treatment-related mortality in all doses tested. Reversible salivation, hyperactivity, and diarrhea were seen in the high-dose d-MPH and d,l-MPH groups. Significant body weight loss and reduction in food consumption were observed in males for both high-dose groups with weights comparable to control values by the end of the recovery period. There were no abnormal clinical pathology or macroscopic or microscopic findings. Based on body weight changes, the no-observed-adverse-effect level (NOAEL) of d-MPH in beagle dogs was 3 mg/kg/day.

Descriptors: pharmacology, toxicology, veterinary medicine, medical sciences, attention deficit hyperactivity disorder, ADHD, (Attention Deficit Disorder with Hyperactivity), behavioral and mental disorders, digestive system disease, oral gavage toxicity study, clinical techniques, body weight loss, food consumption.

Thompson, K., R.T. Thompson, J. Sykes, and G. Wisenberg (2003). **Long-term magnetic resonance imaging/spectroscopy study of cariporide in a canine cardiac ischemia/reperfusion model.** *Journal of Cardiovascular Pharmacology* 41(4): 536-543. ISSN: 0160-2446.

Abstract: Using both 31P and 1H cardiac magnetic resonance techniques, it is possible to monitor the functional (ejection fraction (EF)) and biochemical (pH) status of the heart following a reperfused ischemic insult. This study assessed the effects of Na+/H+ exchange inhibition with cariporide in a closed-chest canine ischemia/reperfusion model. Dogs received 1-mg/kg cariporide treatments for 3 days after occlusion, but were monitored for 10 days. Baseline intracellular pH (+-SEM) for the control and treated groups were 7.10 +- 0.03 and 7.14 +- 0.04, respectively, and dropped to 6.25 +- 0.08 and 6.38 +- 0.08 during occlusion. There was a significant increase in pH from occlusion to early reperfusion in the control group (P = 0.03) but, during the same time period, this increase was not seen in the cariporide group. There was a significant (P = 0.01) drug interaction in recovery of EF over the 10-day protocol. Individual time-point analysis revealed significant differences at immediate reperfusion through day 3 (73.9% +- 2.5%, 84.5% +- 3.1%; baseline normalized EF controls and cariporide, respectively). Neither pH nor EF measurements were significantly different between the groups at day 10. Despite early functional and metabolic benefits, infarct size, as measured at day 10, was 13.2% +- 2.2% for the controls and 11.8% +- 2.3% for the

cariporide group (NS). Thus there were no long-term cariporide functional or biochemical benefits.

Descriptors: cardiovascular system, transport and circulation, methods and techniques, pharmacology, cardiac ischemia reperfusion injury, heart disease, injury, vascular disease, magnetic resonance imaging, imaging and microscopy techniques, laboratory techniques, magnetic resonance spectroscopy, spectrum analysis techniques, ejection fraction, intracellular ph, long term study, sodium ion proton exchange.

Tica, V.I., V. Nestianu, A.A. Tica, M. Beghim, L. Serbanescu, E. Beghim, and S. Bafani (2007). **Cercetari experimentale privind utilizarea piritramidei ca analgezic intratecal. [Experimental study of the use of piritramide as intrathecal analgesic]**. *Chirurgia Bucharest, Romania 1990* 102(1): 57-63. ISSN: 1221-9118.

Abstract: Opioids proved their advantages as general and intrathecal (i.t.) analgesics. Piritramide (P), a largely used analgesic opioid today, has not been studied in i.t. administration. Our experimental research aimed in determining the efficiency, security and optimal dose of i.t. P. In 9 adult mongrel dogs equally randomized in 3 groups we injected i.t. P 1.3 mg x kg-l (group 1), P 0.8 mg x kg-l (group 2) and sodium chloride 0,9% (group 3) and we registered the motility, the pain reaction to electrical and mechanical nociceptive stimuli, the respiratory rate and amplitude, electrocardiogram, heart rate, mean arterial blood pressure electroencephalogram and, for 2 subjects from group 1, electromyogram. The P-induced analgesia was strong, dose-dependent, and segmental, with a time of onset of 5-8 min, duration of 1h 45 min-2h 30 min, and prolonged residual analgesic level for 5-6 h. The dogs from the 1st group presented moderate side effects: bradypnea, tachycardia and arterial hypotension at 5 min, reduction in the posterior limbs motility, sleep. We could conclude that i.t. piritramide 0.8 mg x kg-l provides a solid, segmental, long-lasting analgesia, without marked adverse effects.

Descriptors: analgesics, opioid therapeutic use, pain drug therapy, pirinitramide therapeutic use, analgesics, opioid pharmacology, dogs, injections, spinal, models, animal, pirinitramide pharmacology, random allocation, respiration drug effects.

Language of Text: Romanian-Rumanian; Non-.

Tomiyama, Y., M. Murakami, Y. Yamazaki, M. Kojima, and M. Akahane (2003). **Comparison between cl-316243- and cgp-12177a-induced relaxations in isolated canine ureter.** *Pharmacology* 68(3): 140-146. ISSN: 0031-7012.

NAL Call Number: RM1.P473

Abstract: We compared the effects of CL-316243, a selective beta3-adrenoceptor agonist, and CGP-12177A, a nonconventional partial beta-adrenoceptor agonist, on the KCl-induced contraction in the isolated canine ureter. CL-316243 concentration dependently relaxed the ureteral contraction, the pD2 value being 7.75 +- 0.11. This relaxation was competitively antagonized by the selective beta3-adrenoceptor antagonist SR58894A and by the nonselective beta-adrenoceptor antagonist bupranolol, their pA2 values being 7.08 +- 0.08 and 6.43 +- 0.09, respectively. CGP-12177A concentration dependently reduced the KCl-induced contraction, the pD2 value being 6.30 +- 0.25. Even at 1 X 10-5 mol/l, CGP-20712A (a selective beta1-adrenoceptor antagonist) did not shift the concentration-response curves for CL-316243 or CGP-12177A. SR58894A did not induce a parallel rightward shift in the

concentration-response curve for CGP-12177A, but bupranolol did produce such a shift, pA2 and slope values in the Schild plot being 7.15 +- 0.77 and 0.60 +- 0.15, respectively. Hence, the competition characteristics for SR58894A and bupranolol differed between the CL-316243-induced and CGP-12177A-induced relaxations. Our results suggest that CGP-12177A produces ureteral relaxation in the dog via an atypical beta-adrenoceptor (possibly, an atypical site/state of the beta3-adrenoceptor) as well as via the typical beta3-adrenoceptor.
Descriptors: biochemistry and molecular biophysics, pharmacology, urinary system, chemical coordination and homeostasis, concentration response curves.

Tontodonati, M., N. Fasdelli, E. Moscardo, A. Giarola, and R. Dorigatti (2007). **A canine model used to simultaneously assess potential neurobehavioural and cardiovascular effects of candidate drugs.** *Journal of Pharmacological and Toxicological Methods* 56(2): 265-75. ISSN: 1056-8719.
NAL Call Number: QP901.J6
Abstract: INTRODUCTION: Unwanted effects of drugs on neurobehavioural and cardiovascular functions are normally assessed in separate studies and using different animals. A new model using dogs which allows for the integration of these assessments into a single study was established and validated, adopting the most sophisticated technologies for both monitoring behaviour by video recordings and cardiovascular parameters by telemetry. METHODS: Conscious male beagle dogs (n=4) were given single oral doses of vehicle, and D-amphetamine (0.25, 0.75, 1.5 mg/kg) or acepromazine (0.05, 0.3, 2 mg/kg) within two different studies. Blood pressure, heart rate, electrocardiogram (EKG), body temperature, motor activity and behaviour (by video) were monitored continuously for 24 h post-dose. Animals underwent a full neurobehavioural examination the day before dosing, at the time to the maximal plasma concentration (Tmax) and 24 h post-dose. RESULTS: D-Amphetamine: a dose-dependent increase in arterial blood pressure was noted at all doses and was generally associated with an increase in the QA interval, an index of cardiac contractility. Heart rate also increased but only at the 1.5 mg/kg dose. A dose-dependent general excitatory state of the nervous system was observed, characterised mainly by hyper-reactivity, and stereotyped activities. Acepromazine: a decrease in systolic blood pressure was detected at 0.3 and 2 mg/kg generally associated with a decrease in pulse pressure reflecting a negative inotropic effect. A dose-related increase in heart rate accompanied this effect. Dose-dependent general depression of the nervous system was noted; mainly characterised by half-closed eyes, subdued behaviour and impaired posture. In both studies, all dogs completely recovered at approximately 16 h after treatment. DISCUSSION: Cardiovascular and neurobehavioural changes expected from the pharmacology of test substances were accurately detected. No significant fluctuations of the telemetric parameters recorded were noted as a consequence of the handling associated with the direct neurobehavioural examination. These results confirm the validity of this combined model capable of providing a reliable neurobehavioural and cardiovascular assessment of drugs.
Descriptors: behavior, animal drug effects, cardiovascular physiological phenomena drug effects, drugs, investigational pharmacology, models, animal, acepromazine administration and dosage, acepromazine pharmacology, acepromazine toxicity, administration, oral, behavior, animal physiology, blood pressure drug effects, body temperature drug effects, body temperature physiology, dextroamphetamine administration and dosage, dextroamphetamine

pharmacology, dextroamphetamine toxicity, dogs, dose response relationship, drug, drugs, investigational administration and dosage, drugs, investigational toxicity, electrocardiography drug effects, electrocardiography methods, heart rate drug effects, hyperkinesis chemically induced, hyperkinesis physiopathology, hypnotics and sedatives administration and dosage, hypnotics and sedatives pharmacology, hypnotics and sedatives toxicity, long qt syndrome chemically induced, long qt syndrome physiopathology, motor activity drug effects, motor activity physiology, reflex, pupillary drug effects, reflex, pupillary physiology, reproducibility of results, sialorrhea chemically induced, sialorrhea physiopathology, telemetry methods.

Trott, D.J., L.J. Filippich, J.C. Bensink, M.T. Downs, S.E. Mckenzie, K.M. Townsend, S.M. Moss, and J.J.C. Chin (2004). **Canine model for investigating the impact of oral enrofloxacin on commensal coliforms and colonization with multidrug-resistant escherichia coli**. *Journal of Medical Microbiology* 53(5): 439-443. ISSN: 0022-2615.
NAL Call Number: QR1.J62
Abstract: A model was developed in dogs to determine the impact of oral enrofloxacin administration on the indigenous coliform population in the gastrointestinal tract and subsequent disposition to colonization by a strain of multidrug-resistant Escherichia coli (MDREC). Dogs given a daily oral dose of 5 mg enrofloxacin kg-1 for 21 consecutive days showed a significant decline in faecal coliforms to levels below detectable limits by 72 In of administration. Subsequently, faecal coliforms remained suppressed throughout the period of enrofloxacin dosing. Upon termination of antibiotic administration, the number of excreted faecal coliforms slowly returned over an 8-day period, to levels comparable to those seen prior to antibiotic treatment. Enrofloxacin-treated dogs were more effectively colonized by MDREC, evidenced by a significantly increased count of MDREC in the faeces (7.1 +/- 1.5 log10 g-1) compared with non-antibiotic-treated dogs (5.2 +/- 1.2; P = 0.003). Furthermore, antibiotic treatment also sustained a significantly longer period of MDREC excretion in the faeces (26.8 +/- 10.5 days) compared with animals not treated with enrofloxacin (8.5 +/- 5.4 days; P = 0.0215). These results confirm the importance of sustained delivery of an antimicrobial agent to maintain and expand the colonization potential of drug-resistant bacteria in vivo, achieved in part by reducing the competing commensal coliforms in the gastrointestinal tract to below detectable levels in the faeces. Without in vivo antimicrobial selection pressure, commensal coliforms dominated the gastrointestinal tract at the expense of the MDREC population. Conceivably, the model developed could be used to test the efficacy of novel non-antibiotic strategies aimed at monitoring and controlling gastrointestinal colonization by multidrug-resistant members of the Enterobacteriaceae that cause nosocomial infections.
Descriptors: digestive system, ingestion and assimilation, infection, pharmacology, antibacterial therapy, clinical techniques, therapeutic and prophylactic techniques, oral drug therapy, clinical techniques, therapeutic and prophylactic techniques, bacterial colonization, medical microbiology, methodology, nosocomial infections, sources .

Willigers, H.M., F.W. Prinzen, P.M. Roekaerts, S. De Lange, and M.E. Durieux (2003). **Dexmedetomidine decreases perioperative myocardial lactate release in dogs.** *Anesthesia and Analgesia* 96(3): 657-664. ISSN: 0003-2999.
Abstract: The sympatholytic effect of the alpha2-adrenergic agonist dexmedetomidine may decrease emergence-related myocardial ischemic load in patients. However, a direct measure

of myocardial ischemia, such as myocardial lactate release, is difficult to obtain in patients. Therefore, we studied mongrel dogs and measured myocardial lactate release, myocardial oxygen supply, hemodynamic variables, and neurohumoral indices of the stress response. After the induction of a standardized degree of borderline myocardial ischemia, either dexmedetomidine (dexmed group, n = 9) or normal saline (control group, n = 9) was infused. Measurements were repeated at the end of the anesthetic period and every 10 min during the 90-min emergence period. In the dexmed group, the cumulative emergence-related lactate release was 46% less than in the control group (95% confidence interval, 20%-80%; P = 0.02). Simultaneously, dexmedetomidine increased the endo-/epicardial blood flow ratio by 35% (control group, 0.4 +- 0.1; dexmed group, 0.6 +- 0.1; P = 0.03). These antiischemic effects of dexmedetomidine were accompanied by reduced plasma concentrations of norepinephrine (126 versus 577 pg/mL) and epinephrine (158 versus 1909 pg/mL) and a slower heart rate (123 +- 6 versus 160 +- 10 bpm, dexmed versus control). The antiischemic effect of dexmedetomidine started before emergence, as evidenced by a decreased prevalence of myocardial lactate release at that time (zero of eight dogs in the dexmed group and four of seven dogs in the control group had lactate release before emergence; P = 0.03).
Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, myocardial ischemia, heart disease, vascular disease.

Wilson, J.E., N.V. Chandrasekharan, K.D. Westover, K.B. Eager, and D.L. Simmons (2004). **Determination of expression of cyclooxygenase-1 and -2 isozymes in canine tissues and their differential sensitivity to nonsteroidal anti-inflammatory drugs**. *American Journal of Veterinary Research* 65(6): 810-818. ISSN: 0002-9645.
NAL Call Number: 41.8 Am3A
Abstract: Objective-To evaluate cyclooxygenase isozyme distribution in tissues from dogs and determine the differential sensitivity of canine cyclooxygenase (COX)-1 and -2 isozymes to nonsteroidal anti-inflammatory drugs (NSAIDs). Sample Population-Canine tissue samples (stomach, duodenum, ileum, jejunum, colon, spleen, cerebral cortex, lung, ovary, kidney, and liver) were obtained from 2 dogs for northern and western blot analyses, and blood for whole blood COX assays was obtained from 15 dogs. Procedure-11 NSAIDs were evaluated to determine their COX-2 selectivity in whole blood assays. The concentrations of the drug needed to inhibit 50% of enzyme activity (IC50) were then calculated for comparison. Expression and tissue distribution of COX isozymes were determined by northern and western blot analysis. Results-Aspirin, diclofenac, indomethacin, ketoprofen, meclofenamic acid, and piroxicam had little selectivity toward COX isozymes, whereas NS398, carprofen, tolfenamic acid, nimesulide, and etodolac had more than 5 times greater preference for inhibiting COX-2 than COX-1. All canine tissues examined, including those from the gastrointestinal tract, coexpressed COX-1 and -2 mRNA, although protein expression was observed only for COX-1. Conclusions and Clinical Relevance-Canine COX-2 was selectively inhibited by etodolac, nimesulide, and NS398; tolfenamic acid and carprofen also appeared to be preferential COX-2 inhibitors in dogs. The roles of COX-1 as a constitutive housekeeping enzyme and COX-2 as a proinflammatory inducible enzyme (as determined in humans) appear to apply to dogs; therefore, COX-2-selective inhibitors should prove useful in reducing the adverse effects associated with nonselective NSAIDs.
Descriptors: enzymology, biochemistry and molecular biophysics, pharmacology, cox assay,

bioassay techniques, northern blot analysis, genetic techniques, laboratory techniques, western blot analysis, inhibition constant 50, ic 50.

Xu, H.B. and Z.Q. Huang (2007). **Vasorelaxant effects of icariin on isolated canine coronary artery.** *Journal of Cardiovascular Pharmacology* 49(4): 207-13. ISSN: 0160-2446.
Abstract: Owing to its cardiovascular therapeutical effects, icariin, a flavonoid isolated from Epimedii herba, is considered to be the major active constituent of Epimedii herba. The aim of this study is to investigate the effect of icariin on precontracted coronary artery isolated from canine. Coronary artery segments were isolated from normal anesthetized Beagle dogs and cut into 5-mm rings. The rings were mounted in an organ chamber and contracted by either 40 mM KCl or 10 microM PGF2alpha, and vasorelaxant tone to icariin was measured. Treatment of icariin could significantly produce a relaxation of precontracted coronary arterial rings with intact endothelium in a concentration-dependent manner. Comparatively, the vasorelaxation disappeared in denuded-endothelium rings. Furthermore, the vasorelaxant effect of icariin was blocked by Nomega-Nitro- L-arginine Methyl Ester (L-NAME), 1H-[1, 2, 4]-oxadiazolo [4, 3-a] quinoxalin-1-one (ODQ) but not by indomethacin and glibenclamide, respectively. Tetraethylammonium (TEA) could partly antagonize the vasorelaxant effect triggered by icariin. There was no significant gene expression difference of the endothelial nitric oxide synthase (eNOS) gene in coronary arterial rings among the different concentrations of icariin by RT-PCR, but the activity of eNOS was increased in a concentration-dependent manner after icariin exposure. These results suggest that icariin produces NO-dependent relaxation in the isolated canine coronary artery, and the possible mechanism is involved in the activation of eNOS protein and NO-cGMP pathway.
Descriptors: coronary vessels drug effects, drugs, chinese herbal pharmacology, flavonoids pharmacology, vasodilation drug effects, analysis of variance, anti arrhythmia agents pharmacology, coronary vessels enzymology, coronary vessels physiopathology, dinoprost pharmacology, dogs, dose response relationship, drug, endothelium, vascular drug effects, endothelium, vascular enzymology, endothelium, vascular physiopathology, enzyme inhibitors pharmacology, glyburide pharmacology, indomethacin pharmacology, models, animal, ng nitroarginine methyl ester pharmacology, nitric oxide synthase type iii drug effects, nitric oxide synthase type iii genetics, nitric oxide synthase type iii metabolism, oxadiazoles pharmacology, oxytocics pharmacology, potassium channel blockers pharmacology, quinoxalines pharmacology, rna, messenger drug effects, rna, messenger metabolism, reverse transcriptase polymerase chain reaction, tetraethylammonium pharmacology, vasodilation genetics.

Yaksh, T.L., N. Tozier, K.A. Horais, S. Malkmus, M. Rathbun, L. Lafranco, and J. Eisenach (2008). **Toxicology profile of N-methyl-D-aspartate antagonists delivered by intrathecal infusion in the canine model.** *Anesthesiology* 108(5): 938-49.
Abstract: BACKGROUND: Intrathecal N-methyl-d-aspartate antagonists have antihyperalgesic efficacy. The authors examined toxicity in a canine model of chronic lumbar intrathecal infusion. METHODS: Dogs (10-16 kg) were prepared with lumbar intrathecal catheters connected to vest-mounted pumps (100 microl/h). In phase 1, stepwise incrementations in infusion concentration were performed at 48- to 72-h intervals to determine an infusion dose with minimal but detectable behavioral effects. In phase 2, the dose/concentration defined in phase 1 was infused for 28 days. Behavioral function during infusion and histopathology at

sacrifice was assessed. Drugs examined were 2-amino-5-phosphono-valorate (AP5), MK801, memantine, amitriptyline, S-methadone, and saline. RESULTS: In the phase 1 dose ranging, the minimum effect doses for the several agents were as follows: AP5, 1 mg/day; amitriptyline, 1 mg/day; ketamine, 10 mg/day; MK801, 1 mg/day; and memantine, 4 mg/day. In phase 2, infusion of these doses typically resulted in mild hind limb weakness by 3-5 days after initiation of infusion, which progressed over the 28-day infusion interval. In a limited number of animals, a similar effect was observed with S-methadone. Histopathologically, vehicle-infused animals displayed a minor local catheter reaction. With the drug treatments, a gradient of increasing pathology from cervical to lumbar segments was noted. Pathology ranged from local demyelination to necrotizing lesions of spinal parenchyma near the catheter tip. All drugs given at their respective doses produced pathology scores significantly worse than saline controls. CONCLUSIONS: These drugs given for 28 days at acutely tolerable doses lead to spinal pathology. These data suggest a reevaluation of the use of these agents in chronic spinal delivery.

Descriptors: dizocilpine maleate pharmacology, ketamine pharmacology, n methylaspartate antagonists and inhibitors, amitriptyline administration and dosage, amitriptyline pharmacology, dizocilpine maleate administration and dosage, dogs, infusion pumps, implantable, infusions, parenteral, ketamine administration and dosage, memantine administration and dosage, memantine pharmacology, models, animal, sulfamethizole pharmacology.

Yang, X.P. and S. Chiba (2003). **Interaction between neuropeptide y y1 receptors and alpha1b-adrenoceptors in the neurovascular junction of canine splenic arteries.** *European Journal of Pharmacology* 466(3): 311-315. ISSN: 0014-2999.

NAL Call Number: QP901.E8

Abstract: Previous study has demonstrated that periarterial electrical nerve stimulation (30-s trains of pulses at a frequency of 1 or 4 Hz) induces a double-peaked vasoconstriction consisting of an initial transient, predominantly P2X-receptor-mediated constriction followed by a prolonged, mainly alpha1-adrenoceptor-mediated response in the isolated canine splenic artery. Treatment with 8-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-8-azaspiro(4.5) decane-7,9-dione (BMY 7378, 0.1 mumol/l), a selective alpha1D-adrenoceptor antagonist, produced a slight but significant inhibition of the second peaked responses. A marked inhibition of second peaked responses was obtained by exposure of the tissues to chloroethylclonidine (60 mumol/l), an alpha1B- and alpha1D-adrenoeptor antagonist. Neither BMY 7378 nor chloroethylclonidine affected the first peaked vasoconstrictor responses. (Leu31,Pro34)Neuropeptide Y (10-30 nmol/l), a selective neuropeptide Y Y1 receptor agonist, enhanced the second peaked responses in the presence of BMY 7378 but failed to enhance the responses in the presence of chloroethylclonidine. The results indicate that the postjunctional alpha1B-adrenoceptor subtype is likely coupled to neuropeptide Y Y1 receptors responsible for the cooperation of the sympathetic adrenergic and neuropeptide Yergic transmission in the canine splenic artery.

Descriptors: cardiovascular system, transport and circulation, nervous system, neural coordination, pharmacology .

Yu, S., Y. Ma, T. Xia, and S. Ma (1995). **Studies of action of rhodobrun roseum limpr on changes of red cell aggregation and yield-shear stress in dogs with acute experimental coronary occlusion**. *Zhongguo Zhongyao Zazhi* 20(7): 429-431, 449. ISSN: 1001-5302.
Abstract: Following acute occlusion of the left anterior descending coronary artery in dogs, significant increases were observed in the red cell aggregation index, yield-shear stress and red cell electrophoretic time in blood drained from ischemic area. When transfusion was performed with Rhodobrum roseum solution from the right femoral vein, significant rises of the above-said items were observed.
Descriptors: biochemistry and molecular biophysics, blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, cell biology, pharmacognosy, pharmacology, blood viscosity, myocardial ischemia.
Language of Text: Chinese.

Zaucha, J.M., C. Yu, G. Mathioudakis, K. Seidel, G. Georges, G. Sale, M.T. Little, B. Torok Storb, and R. Storb (2001). **Hematopoietic responses to stress conditions in young dogs compared with elderly dogs**. *Blood* 98(2): 322-327. ISSN: 0006-4971.
NAL Call Number: RB145.A1B57
Abstract: Clinical observations show that older patients do not tolerate high-dose chemoradiotherapy as well as younger patients. It is unclear whether this is due to age-related differences in their responses to hematopoietic injury or to differential toxicities to other organs. In the present study, 6 young (0.5 years) and 6 elderly (8 years) dogs were challenged with 7 repeated nonlethal doses of 50 or 100 cGy total body irradiation (TBI) each (total 550 cGy), and 21 days of recombinant canine granulocyte-colony stimulating factor (rcG-CSF) after the last TBI dose. Recoveries of absolute neutrophil, platelet, and lymphocyte counts after each TBI dose, responses to rcG-CSF treatment, and telomere lengths in neutrophils were compared before and after the study. No differences were found in recoveries of neutrophils, platelets, or in responses to rcG-CSF among young and old dogs. In contrast, recoveries were suggestively worse in younger dogs. After rcG-CSF, platelet recoveries were poor in both groups compared with previous platelet recoveries ($P<.01$). Consequently, 2 old and 3 young dogs were euthanized because of persistent thrombocytopenia and bleeding. At the study's completion, marrow cellularities and peripheral blood counts of the remaining young and elderly dogs were equivalent. The telomere lengths in both groups were significantly reduced after the study versus beforehand ($P=.03$), but the median attritions of telomeres were not different. It was concluded that aging does not appear to affect hematopoietic cell recoveries after repeated low-dose TBI, suggesting that poor tolerance of radiochemotherapy regimens in older patients may be due to nonhematopoietic organ toxicities rather than age-related changes in hematopoietic stem cells reserves.
Descriptors: aging, pharmacology, radiation biology, blood and lymphatics, transport and circulation, thrombocytopenia, blood and lymphatic disease, radiochemotherapy, radiologic method, therapeutic method, bleeding, hematopoietic responses, stress conditions, total body irradiation.

Zhang, J., Z. Chen, F.R. Cobb, and J.S. Stamler (2004). **Role of mitochondrial aldehyde dehydrogenase in nitroglycerin-induced vasodilation of coronary and systemic vessels - an intact canine model**. *Circulation* 110(6): 750-755. ISSN: 0009-7322.

NAL Call Number: RC681.A1 C8
Abstract: Background-It has recently been shown that mitochondrial aldehyde dehydrogenase 2 (mtALDH) catalyzes the formation of 1,2-glyceryl dinitrate and nitrite from nitroglycerin (glyceryl trinitrate (GTN)) within mitochondria, leading to production of cGMP and vasorelaxation. However, whether this mechanism operates in the systemic and coronary beds that subserve the antianginal action of GTN is not known. In this study, we address this question in an intact canine model. Methods and Results-Fourteen healthy mongrel dogs (weight, 20 to 25 kg) were studied. Coronary blood flow and hemodynamics were continuously monitored by a pulse Doppler flow probe implanted around the left circumflex coronary artery and with catheters in left ventricle and aorta, respectively. Each dog was given a 1-mL bolus injection of GTN, sodium nitroprusside (SNP), or adenosine through a catheter in the left atrium before and 30 minutes after infusion of cyanamide (17 mg/kg), an inhibitor of mtALDH. Cyanamide significantly inhibited both the classic dehydrogenase and GTN reductase activities of mtALDH in situ and attenuated the coronary blood flow increase and declines in blood pressure and left ventricular end-diastolic pressure produced by GTN in vivo. In contrast, mtALDH inhibition had no effect on the coronary and systemic effects of SNP and adenosine. Conclusions-Our data suggest that mtALDH contributes to GTN biotransformation in vivo and thus at least partly underlies the antianginal mechanism of drug action. Our findings also highlight the differences in biometabolism of clinically relevant nitrosovasodilators.
Descriptors: cardiovascular system, transport and circulation, pharmacology .

Zhu, B.M., S. Miyamoto, Y. Nagasawa, T. Wajima, and K. Hashimoto (2003). **Effect of the sarcolemmal katp channel blocker hmr1098 on arrhythmias induced by programmed electrical stimulation in canine old myocardial infarction model: comparison with glibenclamide.** *Journal of Pharmacological Sciences* 93(1): 106-113. ISSN: 1347-8613.
Abstract: The blockade of myocardial KATP channels may be antiarrhythmic for ischemic arrhythmias. A new sulfonylthiourea, HMR1098 (1-(15-(2-(5-chloro-o-anisamido) ethyl)-2-methoxyphenylsulfonyl)-3-methylthiourea, sodium salt), was demonstrated to be a cardioselective KATP-channel antagonist and to suppress arrhythmias during acute ischemia. We investigated effects of HMR1098 on the arrhythmias induced by programmed electrical stimulation (PES) in a canine old myocardial infarction model. HMR1098 (3 mg/kg, i.v.) significantly improved the scores of PES-induced ventricular arrhythmias, without changing the blood glucose concentrations. A classical sulfonylurea, glibenclamide (1 mg/kg, i.v.), had no significant effects on these arrhythmias, but reduced the blood glucose and increased the plasma insulin concentrations.
Descriptors: cardiovascular system, transport and circulation, pharmacology, ischemic arrhythmia, heart disease, vascular disease, old myocardial infarction, heart disease, programmed electrical stimulation induced ventricular arrhythmia, heart disease.

Zuperku, E.J., I.F. Brandes, A.G. Stucke, A. Sanchez, F.A. Hopp, and E.A. Stuth (2008). **Major components of endogenous neurotransmission underlying the discharge activity of hypoglossal motoneurons in vivo.** *Advances in Experimental Medicine and Biology* 605: 279-84. ISSN: 0065-2598.
NAL Call Number: QP901 .A33

Abstract: Multibarrel micropipettes were used to simultaneously record unit activity and apply antagonists on individual inspiratory hypoglossal motoneurons (IHMNs) to determine the endogenous activation levels of NMDA, non-NMDA, GABA(A) and serotonin receptors responsible for the IHMN spontaneous discharge patterns in decerebrate dogs. IHMN activity is highly dependent on glutamatergic phasic and tonic drives, which are differentially mediated by the receptor subtypes. Endogenous serotonin significantly amplifies IHMN activity, while GABAergic gain modulation acts to attenuate activity. Thus, alterations in the neurotransmission of any of these systems could markedly alter neuronal output to target muscles.
Descriptors: hypoglossal nerve physiology, motor neurons physiology, synaptic transmission physiology, 2 amino 5 phosphonovalerate pharmacology, bicuculline pharmacology, decerebrate state, dogs, excitatory amino acid antagonists pharmacology, ketanserin pharmacology, models, animal, models, neurological, quinoxalines pharmacology, tongue innervation.

Reproductive System

Lai, C.L., R. van den Ham, G. van Leenders, J. van der Lugt, and E. Teske (2008). **Comparative characterization of the canine normal prostate in intact and castrated animals.** *Prostate* 68(5): 498-507. ISSN: 0270-4137.

Abstract: BACKGROUND: Prostate diseases in the dog are generally regarded as representative for their human counterparts. We characterized the normal canine prostate in comparison to the normal human prostate. METHODS: Prostates of dogs were examined histomorphologically and by immunohistochemical detection of the markers CK14, HMWCK, CK5, CK18, CK7, UPIII, PSA, and PSMA. RESULTS: Histomorphologically, the canine prostate lacks the human zonal differentiation, has much more prominent acini, while comprising less stromal tissue. In general, the canine prostate epithelium displayed a highly differentiated character, with no cells expressing CK14, minimal amounts of cells expressing HMWCK/CK5 and the vast majority of cells expressing CK18 and PSA. After castration, the prostate epithelium regressed, and the remaining tubules were largely populated by cells showing a ductal phenotype (HMWCK+/CK5+/CK18+/CK7+). CONCLUSIONS: The human and canine prostate are histologically differently organized. The general scheme of cellular differentiation of the prostate epithelium may however be applicable to both species.

Descriptors: keratin 18 metabolism, keratin 5 metabolism, keratin 7 metabolism, orchiectomy veterinary, prostate metabolism, prostate pathology, prostate specific antigen metabolism, biological markers metabolism, cell differentiation, dogs, epithelial cells metabolism, epithelial cells pathology, models, animal, phenotype.

Liu, J.B., G. Wansaicheong, D.A. Merton, S.Y. Chiou, Y. Sun, K. Li, F. Forsberg, P.R. Edmonds, L. Needleman, and E.J. Halpern (2008). **Canine prostate: contrast-enhanced US-guided radiofrequency ablation with urethral and neurovascular cooling--initial experience.** *Radiology* 247(3): 717-25.

Abstract: PURPOSE: To prospectively evaluate in a canine model contrast material-enhanced ultrasonography (US) for guiding and monitoring radiofrequency (RF) ablation of the entire prostate, with urethral and vascular cooling to protect the surrounding structures. MATERIALS AND METHODS: After approval by the institutional animal use and care committee, an RF electrode was used to ablate the entire prostate in 15 dogs. During ablation, pulse-inversion harmonic US was performed by using an endocavitary probe after an intravenous bolus injection (0.04 mL/kg) and infusion (0.015 muL/kg/min) of a US contrast agent. In group 1 (n = 4), no cooling protection was used during ablation. In group 2 (n = 5), urethral and bladder protection was provided by inserting a 12-F catheter infused with cold saline (8 degrees C +/- 4 [standard deviation]) at a rate of 100 mL/min. In group 3 (n = 6), further protection of the neurovascular bundles (NVBs) was provided by infusing cold saline (8 degrees C +/- 4) into the iliac arteries at a rate of 50 mL/min by means of catheterization of the femoral artery. Pathologic findings among the three groups were compared by using the Wilcoxon rank sum test. RESULTS: The average volumes of prostate

ablation achieved in the three groups were 96.6%, 91.9%, and 92%. Contrast-enhanced pulse-inversion harmonic US allowed visualization and monitoring of urethral and NVB blood flow during the ablation. Without protection, damage to the urethra and the NVB was demonstrated at both US and pathologic examination. There was highly significant difference in urethral damage between groups with and the group without urethral cooling (P = .002), while intraarterial cooling demonstrated a nonsignificant trend toward a decreased NVB damage (P = .069). CONCLUSION: Contrast-enhanced US can guide RF ablation of the entire prostate. Infusion of cold saline provides effective protection for the urethra during such procedures. The application of intraarterial cooling did not provide a significant improvement in the protection of the NVB in this small study. (c) RSNA, 2008.
Descriptors: catheter ablation, prostate surgery, ultrasonography, interventional, cold temperature, contrast media administration and dosage, dogs, ferric compounds administration and dosage, iron administration and dosage, models, animal, oxides administration and dosage, prospective studies, prostate ultrasonography, rectum, saline solution, hypertonic administration and dosage, statistics, nonparametric, urethra injuries.

Shafik, A. (2008). **An experimental study on the effect of different types of textiles on conception.** *Journal of Obstetrics and Gynaecology the Journal of the Institute of Obstetrics and Gynaecology* 28(2): 213-6.
Abstract: To study the effect of different types of textiles on conception. A total of 35 female dogs were divided into five equal groups: four test and one control. Each of the four test groups was dressed in one type of textile underpants made of either 100% polyester, 50/50% polyester-cotton mix, 100% cotton, or 100% wool. The pants were worn for 12 months. The dogs were followed during this period and for 6 months after removal of the pants by measuring the serum oestradiol 17beta and progesterone and by mating. Electrostatic potentials were also measured on the textile-covered skin. Eight bitches wearing polyester-containing textile showed diminished serum progesterone in the oestrus of the oestrous cycle, and did not conceive on mating or insemination. Five months after pants had been removed, serum progesterone of the eight dogs had normalised, and they conceived. Electrostatic potentials were detected on the skin of all dogs dressed in polyester-containing textile. The low serum progesterone and non-conception of the eight dogs could point to anovulation and failure of luteinisation. It is suggested that the electrostatic potentials detected on the skin create an 'electrostatic field' that inhibits the ovarian function. However, the effect proved to be reversible.
Descriptors: fertilization, polyesters, textiles, dogs, estradiol blood, models, animal, progesterone blood, static electricity.

Silva, F.C., E. Hatschbach, A.F. Lima, Y.K. Carvalho, and F. Massone (2007). **Continuous infusion in adult females dogs submitted to ovariohysterectomy with midazolam-xylazine and/or medetomidine pre-treated with methotrimeprazine and buprenorphine.** *Acta Cirurgica Brasileira Sociedade Brasileira Para Desenvolvimento Pesquisa Em Cirurgia* 22(4): 272-8. ISSN: 0102-8650.
Abstract: PURPOSE: To compare, by continuous infusion of ketamine or medetomidine combined to methotrimeprazine and buprenorphine, ketamine and midazolam, the degree of

hypnosis, myorelaxation, anesthetic quality and surgical feasibility through evaluation of possible parametric alterations and recovery quality. METHODS: 20 healthy adult females dogs, aged 3 to 5 years, body weight between 7 and 15 kg, were assigned randomly and homogenously to 2 groups of 10 animals each (n=10), group 1 (G1) and group 2 (G2), respectively. Animals of G1 were subjected to a pre-treatment with intravenous 1.0 mg/kg methotrimeprazine and or 3i/kg. After 15 minutes, a 5.0 mg/kg ketamine and 0.2 mg/kg midazolam were intravenously injected. Immediately after induction, an anesthetic combination of 0.4 mg/kg/h midazolam, 20 mg/kg/h ketamine and 1.0 mg/kg/h xylazine, was continuously and intravenously administered for 30 minutes. The same techniques were used in G2 except for the substitution of xylazine for 30ig/kg/h medetomidine. RESULTS: In G1 there was a 1st and 2nd degree atrioventricular heart block, a longer recovery period and lower quality. In G2 a 1st degree atrioventricular heart block occurred but isolated and ephemeral. CONCLUSIONS: The continuous infusion method, besides reducing drugs utilization, prevented collateral effects allowing a more tranquil recovery with no excitations, both protocols permitted the surgical procedure (ovary-hysterectomy) bringing about a reduction in hypnosis and an accentuated myorelaxation. Xylazine and medetomidine showed a similar pharmacodynamic behavior but with different clinical aspects. The electrocardiographic alterations observed in G2 and in a lower degree in G1 must be well studied. Describers: dogs, ketamine, methotrimeprazine, medetomidine, midazolam and xylazine.

Descriptors: adrenergic alpha agonists administration and dosage, anesthetics, intravenous administration and dosage, hypnotics and sedatives administration and dosage, hysterectomy methods, ovariectomy methods, analgesics, opioid administration and dosage, anesthetics, combined administration and dosage, buprenorphine administration and dosage, dogs, dopamine antagonists administration and dosage, drug evaluation, preclinical, hysterectomy standards, infusion pumps, medetomidine administration and dosage, methotrimeprazine administration and dosage, midazolam administration and dosage, models, animal, ovariectomy standards, random allocation, xylazine administration and dosage.

Respiratory System

Bartoli, C.R., I. Akiyama, K. Okabe, E.A. Diaz, and J.J. Godleski (2008). **Permanent tracheostomy for long-term respiratory studies.** *Journal of Surgical Research* 145(1): 124-9. ISSN: 0022-4804.

Abstract: BACKGROUND: We describe a modified surgical technique for permanent, anterior tracheal-wall stoma for chronic, repeat respiratory studies in trained, conscious dogs. These cannula-free tracheostomies require minimal daily maintenance, permit repeat intubation with endotracheal tubes modified for airflow respiratory measurement, and facilitate up to 6 h continuous administration of aerosol agents during long-term or repeat respiratory studies. METHODS: In 20 dogs, during a 30 to 40 min procedure, portions of tracheal rings 2-4 were removed to create an oval stoma, approximately 2 x 1 cm. The dermis was secured to the transected cartilage and tracheal mucosa in such a manner that skin covered the sternohyoid muscles and grew-in flush with the tracheal mucosa at the stomal opening. Stomas were cleaned daily, and fur was clipped weekly around the stomal site. No other maintenance procedures or environmental modifications were needed. Animals breathed through both the stoma and the upper airway and barked normally. RESULTS: Stomas remained viable in long-term animals (n = 4) ongoing for 70.3 +/- 32.2 mo (mean +/- SEM), with an ongoing maximum of 126 mo. Postmortem examinations were performed on shorter-term animals (n = 16) sacrificed at 16.7 +/- 7.3 mo. Thirteen showed no appreciable tracheal stenosis and three showed <10% stenosis at the level of the stoma. Histopathological examination of the stomal opening and surrounding tissue revealed minimal chronic inflammation and no evidence of necrosis or infection. CONCLUSIONS: During long-term respiratory studies, this practical and dependable tracheal stoma provides a means for examining acute and chronic effects of environmental and pathophysiological influences on the respiratory system of conscious dogs.

Descriptors: surgical stomas pathology, trachea pathology, trachea surgery, tracheostomy methods, aerosols administration and dosage, dogs, inflammation pathology, intubation, intratracheal, models, animal, postoperative care methods, respiratory function tests, respiratory system physiopathology, tracheal stenosis pathology.

Bilotta, F., L. Agati, V. Fabbrini, G. Centola, and G. Rosa (2003). **Pulmonary transit of levovist(r): a transthoracic echocardiographic study.** *2003 Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, USA; October 11-15, 2003,*

Abstract: After intravenous injection in spontaneously breathing patients and anesthetized dogs, ultrasound contrast agents opacify the right ventricle, pass through the lungs, opacify the left ventricle and depict systemic organ perfusion patterns. Contrast ultrasound based intraoperative organ-perfusion studies -- currently limited to intraarterial or intraaortic injection -- require an intravenous ultrasound contrast agent that passes through the lungs during mechanical ventilation in humans. Effective lung transit of ultrasound contrast agents during controlled mechanical ventilation is a prerequisite for ultrasound-based real time systemic organ perfusion studies (myocardium, kidneys, liver and brain) because it allows the con-

trast agent injected intravenously to reach the systemic circulation. Whether an ultrasound contrast agent passes the lungs during mechanical ventilation depends on many factors, including biochemical interactions with blood gasses, intravascular pressure and shell stability. Mechanical ventilation alters the physiology of the pulmonary microcirculation by increasing intrathoracic pressure and pulmonary vascular resistance. Levovist(R) (Schering AG, Berlin, Germany) is a galactose and palmitic based air-filled ultrasound contrast agent used for organ perfusion studies with intravenous injection in spontaneously breathing patients. In this study, we investigated whether Levovist(R) injected intravenously during intermittent positive pressure ventilation (IPPV) opacifies the right and left ventricular cavities after lung transit. With transthoracic echocardiography we measured the time in cardiac cycles (CC), for contrast to appear in the right ventricle and traverse the lungs; and the intensity of right and left ventricular cavity opacification (RVCO and LVCO). Twenty patients undergoing elective peripheral neurosurgical procedures were prospectively enrolled. All patients received intravenous Levovist(R) 1 g, during spontaneous breathing (baseline), 5 min after the beginning of IPPV, and 5 min and 30 min after extubation. Pulmonary transit time was constant: 7 +- 3 CC at baseline, 6 +- 2 CC during IPPV, and 8 +- 2 CC at 5 min and 7 +- 3 CC at 30 min after extubation. In all patients, each of the four contrast injections achieved high-grade RVCO and LVCO, and remained constant before, during IPPV and at 5 and 30 minutes after extubation. In this study, conducted in patients mechanically ventilated during general anesthesia for peripheral neurosurgical procedures, intravenous injection of Levovist(R) during IPPV opacified the right ventricular cavity, passed physiologically through the lungs and opacified the left ventricular cavity. It did so at an intensity equivalent to that when patients breathed spontaneously. During surgery, especially in high-risk patients, adequate organ blood flow is critical for normal cellular metabolism and tissue preservation. Because hypoperfusion often precedes and causes functional damage, early diagnosis of inadequate tissue perfusion could guide treatment to restore perfusion. In conclusion, Levovist(R) injected intravenously provides physiologic pulmonary capillary transit in patients undergoing peripheral neurosurgical procedures during mechanical ventilation. An ultrasound contrast agent with these properties might make real-time echographic evaluation of organ perfusion patterns possible in patients during IPPV. Anesthesiology 2003; 99: A168.
Descriptors: methods and techniques, pharmacology, surgery, medical sciences, contrast ultrasound, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, mechanical ventilation, therapeutic and prophylactic techniques, transthoracic echocardiography, cardiac cycles.

Black, B.A., J.R. Moore, O.B. Wilson, R.D. Hubmayr, and A.M. Boriek (2002). **Mechanics and kinematics of the midcostal diaphragm and lower rib cage in dogs**. *FASEB Journal* 16(5): A878. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: muscular system, movement and support, respiratory system model, beagle dogs, respiration, lung volume, skeletal system, movement and support, meeting abstract.

Blanch, L., T.E. Van der Kloot, A.M. Youngblood, A.B. Adams, A. Naveira, G. Murias, P.V. Romero, and A. Nahum (2001). **Selective tracheal gas insufflation during partial liquid ventilation improves lung function in an animal model of unilateral acute lung injury.** *Critical Care Medicine* 29(12): 2251-7. ISSN: 0090-3493.

Abstract: OBJECTIVE: During unilateral lung injury, we hypothesized that we can improve global lung function by applying selective tracheal gas insufflation (TGI) and partial liquid ventilation (PLV) to the injured lung. DESIGN: Prospective, interventional animal study. SETTING: Animal laboratory in a university hospital. SUBJECTS: Adult mixed-breed dogs. INTERVENTIONS: In six anesthetized dogs, left saline lung lavage was performed until PaO(2)/FiO(2) fell below 100 torr (13.3 kPa). The dogs were then reintubated with a Univent single-lumen endotracheal tube, which incorporates an internal catheter to provide TGI. In a consecutive manner, we studied 1) the application of 10 cm H(2)O of positive end-expiratory pressure (PEEP); 2) instillation of 10 mL/kg of perflubron (Liquivent) to the left lung at a PEEP level of 10 cm H(2)O (PLV+PEEP 10 initial); 3) application of selective TGI (PLV+TGI) while maintaining end-expiratory lung volume (EELV) constant; 4) PLV+TGI at reduced tidal volume (VT); and 5) PLV+PEEP 10 final. MEASUREMENTS AND MAIN RESULTS: Application of PLV+PEEP 10 initial did not change gas exchange, lung mechanics, or hemodynamics. PLV+TGI improved PaO(2)/FiO(2) from 189 +/- 13 torr (25.2 +/- 1.7 kPa) to 383 +/- 44 torr (51.1 +/- 5.9 kPa) (p <.01) and decreased PaCO(2) from 55 +/- 5 torr (7.3 +/- 0.7 kPa) to 30 +/- 2 torr (4.0 +/- 0.3 kPa) (p <.01). During ventilation with PLV+TGI, reducing VT from 15 mL/kg to 3.5 mL/kg while keeping EELV constant decreased PaO(2)/FiO(2) to 288 +/- 49 torr (38.4 +/- 6.5 kPa) (not significant) and normalized PaCO(2). At this stage, end-inspiratory plateau pressure decreased from 19.2 +/- 0.7 cm H(2)O to 13.6 +/- 0.7 cm H(2)O (p <.01). At PLV+PEEP 10 final, measurements returned to those observed at previous baseline stage (PLV+PEEP 10 initial). CONCLUSIONS: During unilateral lung injury, PLV with a moderate PEEP did not improve oxygenation, TGI superimposed on PLV improved gas exchange, and combination of TGI and PLV allowed a 77% reduction in VT without any adverse effect on PaCO(2).

Descriptors: adult, mixed-breed, lung injury, lung function, tracheal gas insufflation (TGI), partial liquid ventilation (PLV).

Bof, A.M., A. Rapoport, D.N. Paulo, L.C. Leiro, M.R. Gomes, and R.R. Pando Serrano (2007). **Comparative study of the resistance of manual and mechanical sutures in the bronchial stump of dogs submitted to left pneumonectomy.** *Jornal Brasileiro De Pneumologia Publicacao Oficial Da Sociedade Brasileira De Pneumologia e Tisilogia* 33(2): 141-7.

Abstract: OBJECTIVE: To compare the resistance of manual suture with that of mechanical suture immediately after the suture of the left bronchial stump of dogs submitted to pneumonectomy. METHODS: A total of 15 mixed-breed dogs of both genders, each weighing between 8 and 23 kg, were randomly divided into 2 groups. In group I (n = 7), the bronchial stump was sutured manually (the Sweet method) and, in group II (n = 8), it was stapled. Immediately after the closure of the bronchial stump, the intratracheal pressure was progressively increased in a controlled manner. RESULTS: The mean rupture pressure of the bronchial stump suture line was 33.71 mmHg in group I and 89.87 mmHg in group II (p < 0.01). CONCLUSION: These data allowed us to conclude that mechanical suture of the

bronchial stump, submitted to pressure immediately after closure, is more resistant than is manual suture in dogs submitted to pneumonectomy.
Descriptors: bronchi surgery, pneumonectomy methods, suture techniques adverse effects, sutures adverse effects, data interpretation, statistical, dogs, models, animal, pressure, random allocation, surgical stapling.
Language of Text: Portuguese.

Brimioulle, S., V. Julien, R. Gust, J.K. Kozlowski, R. Naeije, and D.P. Schuster (2002). **Importance of hypoxic vasoconstriction in maintaining oxygenation during acute lung injury.** *Critical Care Medicine.* 30(4): 874-80. ISSN: 0090-3493.
Abstract: OBJECTIVE: To investigate the role of hypoxic pulmonary vasoconstriction in the intrapulmonary blood flow redistribution and gas exchange protection during oleic acid acute lung injury. DESIGN: Prospective, controlled animal study. SETTING: Research laboratory of an academic institution. SUBJECTS: Three groups of five mongrel dogs. INTERVENTIONS: Induction of acute lung injury by 0.08 mL/kg oleic acid intravenously. Hypoxic pulmonary vasoconstriction inhibition by Escherichia coli endotoxin microdose (15 microg/kg) pretreatment or by metabolic alkalosis (pH 7.60). MEASUREMENTS AND MAIN RESULTS: Pulmonary arterial and venous resistances were determined by flow-pressure curves and by capillary pressure estimation. Regional lung water and pulmonary blood flow were assessed by positron emission tomography. Oleic acid alone increased the arterial and venous resistances, redistributed blood flow away from edematous areas, and decreased the Pao2 from 507 +/- 16 to 373 +/- 60 torr. on Fio2 1.0 and positive end-expiratory pressure 5 cm H2O. Endotoxin pretreatment inhibited the increase in arterial resistance, suppressed the redistribution, and decreased the Pao2 to 105 +/- 22 torr. Alkalosis inhibited the increase in arterial and venous resistances, suppressed the redistribution, and decreased the Pao2 to 63 +/- 12 torr. Reversal of the alkalosis increased the arterial and venous resistances, restored the perfusion redistribution, and improved the Pao2 to 372 +/- 63 torr. Changes in blood gases conformed to predictions of a computer lung model in which hypoxic pulmonary vasoconstriction was suppressed by endotoxin and alkalosis. CONCLUSIONS: We conclude that in oleic acid-induced lung injury, a) pulmonary hypertension results from increases in both arterial and venous resistances; b) the increase in arterial resistance is the primary mechanism responsible for the perfusion redistribution and the gas exchange protection; and c) the increase in arterial resistance is most consistent with hypoxic pulmonary vasoconstriction.
Descriptors: hypoxic pulmonary vasoconstriction, intrapulmonary blood flow, oleic acid, acute lung injury, arterial resistance, venous resistance.

Brogan, T.V., H.T. Robertson, W.J.E. Lamm, J.E. Souders, and E.R. Swenson (2003). **Effect of inspired co2 on va/q matching in dogs as measured by microspheres.** *Pediatric Research* 53(4 Part 2): 49A. ISSN: 0031-3998.
NAL Call Number: RJ1.P4
Descriptors: respiratory system, respiration, miget, v a, q matching, microspheres, perfusion, sites of action, ventilation .

Cappello, M., C. Yuehua, and A. De Troyer (1995). **Rib cage distortion in a canine model of flail chest**. *American Journal of Respiratory and Critical Care Medicine* 151(5): 1481-1485. ISSN: 1073-449X.

NAL Call Number: RC705 .A4

Abstract: Although blunt chest injuries frequently lead to respiratory failure, the effects of flail chest on the mechanics of breathing have not been evaluated. In the present studies, we have measured the respiratory displacements of the ribs and sternum and the electromyograms (EMG) of the parasternal and external intercostal muscles in eight supine, anesthetized, spontaneously breathing dogs before and after the third to sixth ribs on the right side of the chest were fractured both dorsally and ventrally. After flail, the fractured ribs moved inward, rather than outward, during inspiration, but their inspiratory cranial displacement remained unchanged. The inspiratory outward and caudal displacement of the sternum, the inspiratory EMG activity of the parasternal intercostals, the pattern of breathing, and the arterial blood gases were also unaltered. However, the inspiratory EMG activity recorded from the external intercostals increased consistently to 327 +- 101% of control (p lt 0.05). These observations indicate that with flail chest, the disconnected segment of the rib cage shows paradoxical motion exclusively along the lateral axis; the increased external intercostal activation may account, at least in part, for the persistent inspiratory cranial motion of the ribs. These observations also suggest that the harmful effects of blunt chest injuries are related to pulmonary contusion and pain, rather than to flail chest per se.

Descriptors: animal care, respiratory system, respiration .

Casal, M., S. Ryan, J. Rhodes, and J. Scheidt (2003). **Immunological aspects of x-linked ectodermal dysplasia: a dog model for the human disease.** *American Journal of Human Genetics* 73(5): 454. ISSN: 0002-9297.

NAL Call Number: QH431.A1A54

Descriptors: molecular genetics, biochemistry and molecular biophysics, X linked ectodermal dysplasia, genetic disease, immune system disease, integumentary system disease, respiratory system disease, genetics, immunology, pathology, transmission, pulmonary disorders, respiratory system disease, respiratory tract infection, infectious disease, cytokine production, immune system defects, immunological aspects, systemic, localized humoral, cellular responses.

Chhetri, D.K., B. Jahan Parwar, S.D. Hart, S.M. Bhuta, and G.S. Berke (2004). **Injection laryngoplasty with calcium hydroxylapatite gel implant in an in vivo canine model**. *Annals of Otology Rhinology and Laryngology* 113(4): 259-264. ISSN: 0003-4894.

Abstract: The ideal injectable agent for vocal fold medialization is biocompatible, durable, sized to prevent phagocytosis and migration, and formulated for easy injection and does not adversely affect the viscoelastic properties of the vocal fold. We tested a cohesive implant of calcium hydroxylapatite (CaHA) particles in a gel carrier in an in vivo canine model of phonation. Six dogs underwent unilateral recurrent laryngeal nerve section and injection laryngoplasty of the paralyzed vocal fold with a CaHA implant. The six follow-up examinations were performed at 1, 2, 3, 6, 9, and 12 months, and the larynx and bilateral neck lymphatic system were harvested for histologic analysis. The CaHA implant adequately medialized the vocal fold to regain glottal closure. The mucosal waves remained unaltered from baseline. The

implant remained soft in the larynx and did not migrate to the neck lymphatic system. A localized foreign body giant cell reaction was present on histologic evaluation, but not acute or other chronic inflammation. A size analysis revealed no resorption of the CaHA particles. A decrease in medialization was noted at all follow-up intervals related to resorption of the aqueous-based gel carrier. The CaHA implant appears to be relatively safe and suitable for injection laryngoplasty.
Descriptors: equipment apparatus devices and instrumentation, methods and techniques, nervous system, neural coordination, respiratory system, respiration, calcium hydroxylapatite gel implant, prosthetic, histologic analysis, histology and cytology techniques, laboratory techniques, injection laryngoplasty, clinical techniques, therapeutic and prophylactic techniques, unilateral recurrent laryngeal nerve section, experimental surgical techniques, vocal fold paralysis, experimental surgical techniques, cell migration, phagocytosis, phonation .

Chino, K., C.K. Choong, P.D. Toeniskoetter, J.D. Cooper, H.F. Lausberg, K.T. Bae, and J.A. Pierce (2004). **A canine model for production of severe unilateral panacinar emphysema**. *Experimental Lung Research* 30(4): 319-332. ISSN: 0190-2148.
Abstract: The authors created a canine model of severe emphysema using whole lung lavage to deliver repeated porcine pancreatic elastase solution to the terminal airways and alveoli of the right lung. This model produces extreme unilateral panacinar emphysema closely resembling that encountered in patients with alpha1-antitrypsin deficiency. Because the contralateral lung remains functional, the animals can be maintained indefinitely. The model will be of value in developing imaging techniques capable of safely evaluating the effect of treatment on panacinar emphysema in alpha 1 -antitrypsin-deficient patients.
Descriptors: respiratory system, respiration, unilateral panacinar emphysema, respiratory system disease.

Chu, Y., Y.C. Wu, Y.C. Chou, H.Y. Chueh, H.P. Liu, J.J. Chu, and P.J. Lin (2004). **Endothelium-dependent relaxation of canine pulmonary artery after prolonged lung graft preservation in university of wisconsin solution: role of l-arginine supplementation**. *Journal of Heart and Lung Transplantation* 23(5): 592-598. ISSN: 1053-2498.
Abstract: Background: The University of Wisconsin (UW) solution has been demonstrated to enhance pulmonary allograft preservation. Endothelial nitric oxide (NO) production has been shown to be significantly impaired after ischemia and reperfusion (I/R) injury. The present experiments aimed to determine the protective effects of pulmonary endothelium-dependent function by using supplemental NO in University of Wisconsin (UW) solution following prolonged lung graft preservation. Methods: Thirty-six healthy mongrel dogs underwent thoracotomy to expose the left lung. In addition to a group given UW solution (n = 4), 100 mumol/liter L-arginine, (n = 7), 100 mumol/liter NG-monomethyl-L-arginine (L-NMMA n = 7) and 1.0 mumol/liter 3-morpholinosydnonimine (SIN-1, n = 18 respectively, were added to UW solution, and infused from the aortic root and pulmonary artery to the pulmonary vein. The perfused lung was then allowed to inflate to its maximum volume for 24-hour oxygenated preservation in each supplemented condition of UW solution at 4degreeC. In the SIN-1 group, the preservation period was further divided into 8 hours and 16 hours, respectively. Rings of the third-order pulmonary artery of the inflated lung were then suspended in organ chambers to measure isometric force. Results: Endothelium-

dependent relaxation (EDR) to acetylcholitie, adenosine diphosphate and sodium fluoride of the pulmonary rings in the L-arginine group was significantly preserved compared with UW-solution-only group. The L-NMMA group showed significant EDR impairment after 24-hour preservation compared with the UW solution group. Similar to the L-arginine group, the SIN-1 group showed significant EDR protection with 8-hour preservation, but not with 24-hour preservation. In contrast, EDR to calcium ionophore A23187 showed no EDR changes after 24-hour preservation in any of the supplemented groups. Conclusions: Supplemental L-arginine in UW solution ameliorates impaired pulmonary EDR following prolonged lung preservation of up to 24 hours.
Descriptors: biochemistry and molecular biophysics, cardiovascular system, transport and circulation, respiratory system, respiration, ischemia and reperfusion injury, vascular disease, pathology, prolonged lung graft preservation.

Criner G J , Muza S R , and Kelsen S G (1990). **Inspiratory action on the rib cage by the canine pectoral muscles**. *American Review of Respiratory Disease* 141(4 PART 2): A170. ISSN: 0003-0805.
NAL Call Number: RC705 .A4
Descriptors: muscular system, movement and support, respiratory system, respiration, skeletal system, movement and support, abstract

Dane, D.M., X. Yan, R.M. Tamhane, R.L.J. Johnson, A.S. Estrera, D.C. Hogg, R.T. Hogg, and C.C.W. Hsia (2004). **Retinoic acid-induced alveolar cellular growth does not, improve function after right pneumonectomy.** *Journal of Applied Physiology* 96(3): 1090-1096. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: To determine whether all-trans retinoic acid (RA) treatment enhances lung function during compensatory lung growth in fully mature animals, adult male dogs (n=4) received 2 mgcntdotkg-1cntdotday-1 po RA 4 days/wk beginning the day after right pneumonectomy (R-PNX, 55-58% resection). Litter-matched male R-PNX controls (n=4) received placebo. After 3 mo, transpulmonary pressure (TPP)-lung volume relationship, diffusing capacities for carbon monoxide and nitric oxide, cardiac output, and septal volume (Vtiss-RB) were measured under anesthesia by a rebreathing technique at two lung volumes. Lung air and tissue volumes (Vair-CT and Vtiss-CT) were also measured from high-resolution computerized tomographic (CT) scans at a constant TPP. In RA-treated dogs compared with controls, TPP-lung volume relationships were similar. Diffusing capacities for carbon monoxide and nitric oxide were significantly impaired at a lower lung volume but similar at a high lung volume. Whereas Vtiss-RB was significantly lower at both lung volumes in RA-treated animals, Vair-CT and Vtiss-CT were not different between groups; results suggest uneven distribution of ventilation consistent with distortion of alveolar geometry and/or altered small airway function induced by RA. We conclude that RA does not improve resting pulmonary function during the early months after R-PNX despite histological evidence of its action in enhancing alveolar cellular growth in the remaining lung.
Descriptors: methods and techniques, pharmacology, respiratory system, respiration, right pneumonectomy, experimental surgical techniques, laboratory techniques, alveolar cellular

growth, cardiac output, diffusing capacity for carbon monoxide, lung air, lung function, lung volume, resting pulmonary function, septal volume, tissue volume, transpulmonary pressure.

Decramer M , Reid M B , and De Troyer A (1985). **Relationship between parasternal intercostal length and rib cage displacement in dogs**. *Journal of Applied Physiology* 58(5): 1517-1520. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: The relationship between parasternal intercostal length and rib cage cross-sectional area was examined in 9 supine dogs during passive inflation and during quiet breathing before and after phrenicotomy. Parasternal intercostal length (PSL) was measured with a sonomicrometry technique and rib cage cross-sectional area (Arc) was measured with a Respitrace coil placed around the middle rib cage. During active inspiration as well as during passive inflation, PSL decreased as Arc increased. However, the relationship between PSL and Arc during active inspiration, whether in the intact or phrenicotomized animal, was almost invariably different from that during passive inflation, so that the same increase in Arc was associated with a greater decrease in PSL in the former than in the latter instance. This difference between passive inflation and active inspiration was probably due to the active contraction of the parasternals during inspiration and the consequent caudal displacement of the sternum. In upright humans, the sternum moved cephalad and not caudad during inspiration, so the relationship between PSL and Arc during active breathing might be similar to that during passive inflation.
Descriptors: muscular system, movement and support, nervous system, neural coordination, respiratory system, respiration, surgery, medical sciences, respiratory muscle passive inflation active inspiration.

Denault, A.Y., J.3. Gorcsan, and M.R. Pinsky (2001). **Dynamic effects of positive-pressure ventilation on canine left ventricular pressure-volume relations.** *Journal of Applied Physiology* 91(1): 298-308. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: Positive-pressure ventilation (PPV) may affect left ventricular (LV) performance by altering both LV diastolic compliance and pericardial pressure (Ppc). We measured the effect of PPV on LV intraluminal pressure, Ppc, LV volume, and LV cross-sectional area in 17 acute anesthetized dogs. To account for changes in lung volume independent of changes in Ppc and differences in contractility, measures were made during both open- and closed-chest conditions, during closed chest with and without chest wall binding, and after propranolol-induced acute ventricular failure (AVF). Apneic end-systolic pressure-volume relations (ESPVR) were generated by inferior vena caval occlusions. With the open chest, PPV had no effects. With the chest closed, PPV inspiration decreased LV end-diastolic volume (EDV) along its diastolic compliance curve and decreased end-systolic volume (ESV) such that the end-systolic pressure-volume domain was shifted to a point left of the LV ESPVR, even when referenced to Ppc. The decrease in EDV was greater in control than in AVF conditions, whereas the shift of the ESV to the left of the ESPVR was greater with AVF than in control conditions. We conclude that the hemodynamic effects of PPV inspiration are due primarily to changes in intrathoracic pressure and that the inspiration-induced decreases of LV EDV reflect direct effects of intrathoracic pressure on LV filling. The decreases in LV ESV exceed

the amount explained solely by a reduction in LV ejection pressure.
Descriptors: physiology, positive pressure ventilation, anesthetized dogs, diastolic pressure, pericardial pressure, intraluminal pressure.

Dias Junior, C.A., J.T. Sertorio, and J.E. Tanus Santos (2007). **Aminoguanidine produces beneficial haemodynamic effects in a canine model of acute pulmonary thromboembolism.** *Acta Physiologica Oxford, England* 191(3): 189-96. ISSN: 1748-1708.
NAL Call Number: QP1 .A2
Abstract: AIM: Activating the nitric oxide (NO)-cyclic guanosine 3',5'-monophosphate (cGMP) pathway improves haemodynamics following acute pulmonary thromboembolism (APT). However, the role of NO synthase (NOS) isoforms in the responses to APT has not been determined. We examined the effects of selective and non-selective inducible NOS (iNOS) inhibition. METHODS: Haemodynamic evaluations were performed in non-embolized dogs treated with saline (control group; n = 4), L-NAME (NAME group; n = 3), or aminoguanidine (AG group; n = 3), and in dogs that received the same drugs and were embolized with 5 mL kg(-1) of clots made with autologous blood (Emb group, n = 9; NAME + Emb group, n = 4 and AG + Emb group, n = 7). The lung concentrations of nitrite/nitrate (NOx) and cGMP were determined by chemiluminescence and ELISA respectively. RESULTS: Acute pulmonary thromboembolism increased mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance index (PVRI) by 21.4 +/- 1.7 mmHg and by 843 +/- 34 dyn s cm(-5) m(-2), respectively, in Emb group. MPAP and PVRI increased to higher levels in the NAME + Emb group 15 min after APT and all dogs in this group died 15-30 min after APT. Conversely, lower MPAP and PVRI levels were found in the AG + Emb group 2 h after APT compared with the Emb group (both $P < 0.05$). Higher NOx concentrations were found in the Emb group compared with the other groups (all $P < 0.05$). Higher cGMP concentrations were found in the Emb and AG + Emb groups compared with the other groups (all $P < 0.05$). CONCLUSIONS: These results indicate that endogenous NO protects against APT-induced cardiovascular responses. Moreover, iNOS-derived NO possibly produces unfavourable effects, which are counteracted by aminoguanidine. However, non-NO-related mechanisms may also be involved.
Descriptors: guanidines therapeutic use, nitric oxide synthase type ii antagonists and inhibitors, pulmonary embolism drug therapy, acute disease, blood pressure drug effects, cyclic gmp analysis, cyclic gmp metabolism, dogs, lung chemistry, lung metabolism, models, animal, ng nitroarginine methyl ester metabolism, ng nitroarginine methyl ester therapeutic use, nitrates analysis, nitrates metabolism, nitric oxide metabolism, nitric oxide synthase type ii metabolism, pulmonary embolism metabolism, vascular resistance drug effects.

Downie, J.M., A.J. Nam, and B.A. Simon (2004). **Pressure-volume curve does not predict steady-state lung volume in canine lavaae lung injury**. *American Journal of Respiratory and Critical Care Medicine* 169(8): 957-962. ISSN: 1073-449X.
NAL Call Number: RC705 .A4
Abstract: To better understand strategies for recruiting and maintaining lung volume in acute lung injury, we examined relationships between steady-state lung volume and cumulative cyclic recruitment/ derecruitment volume history and the quasi-static pressure-volume curve, in an animal saline lavage lung injury model. Small-volume tidal pressure-volume

loops performed after inflation from functional residual capacity demonstrated incremental, cyclic recruitment only if the peak pressure achieved exceeded the pressure at which the compliance increased (Pflex) on the pressure-volume curve, whereas loops performed after deflation from total lung capacity remained close to the envelope deflation curve. Recruitment continued to occur up to and beyond a peak inspiratory airway pressure of 40 cm H2O, as demonstrated by both the tidal loops and by computed tomography-derived lung volume data. Tidal-specific compliance was relatively constant across positive end-expiratory pressure levels after inflation from functional residual capacity, but peaked at moderate positive end-expiratory pressure after deflation from total lung capacity, further demonstrating the effects of volume history and providing experimental validation of the recruitment models of Hickling (AJRCCM 2001;163:69-78). These results support the interpretation of Pflex as pressure threshold for recruitment, but otherwise do not suggest a role for the pressure-volume curve in predicting steady-state lung volume.
Descriptors: respiratory system, respiration, acute lung injury, respiratory system disease, diagnosis, therapy, computed tomography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, mechanical ventilation, therapeutic and prophylactic techniques, positive end expiratory pressure, pressure volume curve.

Ednick, M.D., M. Pagala, J.P. Barakat, G. Nino, P. Shah, J.N.J. Cunningham, M. Vaynblat, and M. Kazachkov (2007). **Telemetric recording of intrapleural pressure.** *Journal of Surgical Research* 138(1): 10-4. ISSN: 0022-4804.
Abstract: BACKGROUND: Monitoring of intrapleural pressure (IPP) is used for evaluation of lung function in a number of pathophysiological conditions. We describe a telemetric method of non-invasive monitoring of the IPP in conscious animals intermittently or continuously for a prolonged period of time. MATERIALS AND METHODS: After IACUC approval, six mongrel dogs were used for the study. After sedation, each dog was intubated and anesthetized using 0.5% Isoflurane. A telemetric implant model TL11M2-D70-PCT from Data Science International was secured subcutaneously. The pressure sensor tip of the catheter from the implant was inserted into the pleural space, and the catheter was secured with sutures. The IPP signals were recorded at a sampling rate of 100 points/second for 30 to 60 min daily for 4 days. From these recordings, the total mean negative IPP (mmHg), and the total mean negative IPP for a standard time of 30 min were calculated. In addition, the actual inspiratory and expiratory pressures were also measured from stable recording of the IPP waveforms. RESULTS: In six dogs, the total mean +/- SD negative IPP was -10.8 +/- 10.6 mmHg. After normalizing with respect to acquisition time it was -13.2 +/- 11.2 mmHg/min. The actual inspiratory pressure was -19.7 +/- 15.3, and the expiratory pressure was -11.0 +/- 12.9. CONCLUSIONS: Our study demonstrates that telemetric monitoring of IPP can be performed reliably and non-invasively in conscious experimental animals. The values for IPP in our study are compatible with the results of other investigators who used different methods of IPP measurement. Further work may show this method to be helpful in understanding the pathophysiology of various breathing disorders.
Descriptors: exhalation physiology, inhalation physiology, manometry instrumentation, pleural cavity physiology, telemetry instrumentation, catheterization, consciousness, dogs, manometry methods, models, animal, motor activity, pressure, telemetry methods.

Glaus, T.M., M. Hassig, C. Baumgartner, and C.E. Reusch (2003). **Pulmonary hypertension induced in dogs by hypoxia at different high-altitude levels.** *Veterinary Research Communications* 27(8): 661-670. ISSN: 0165-7380.

NAL Call Number: SF601 .V38

Abstract: Chronic natural hypoxia at 2300 in altitude induces mild pulmonary hypertension (PH) in healthy dogs. The influence of more severe hypoxia on the same group of dogs was evaluated by re-examining such dogs at 3500 m, after they had regularly exercised at this altitude level for half a year. Despite severe hypoxaemia at 3500 in (PaO2 52+-5 mmHg), none of the dogs developed erythrocytosis, and their PCV at 3500 in (48%+-4%) did not differ from that at 2300 in (49%+-40%). There was a tendency towards an elevated systemic BP, with a significant increase in diastolic BP (105+-13 mmHg at 3500 m versus 98+-17 at 2300 m). Tricuspid regurgitation (TR) was detected in 7 dogs at 3500 m compared to 8 dogs at 2300 m. The mean TR Vmax was significantly higher at 3500 m, and all 7 dogs had systolic PH at 3500 in (33.6-54.8 mmHg), when PH was defined as TR Vmax gtoreq2.8 m/s, i.e. a peak pressure gradient >30 mmHg. Hence, in dogs, increasing altitude and the concomitant hypoxia result in a progressively more pronounced PH and an elevated systemic BP. Intermittent severe hypoxaemia of around 50 mmHg may not cause erythrocytosis in healthy dogs, even over a prolonged period.

Descriptors: blood and lymphatics, transport and circulation, cardiovascular system, transport and circulation, erythrocytosis, polycythemia, pulmonary hypertension, vascular disease, tricuspid regurgitation, heart disease, blood pressure, chronic natural hypoxia, high altitude, packed cell volume.

Harris, S.B., M.G. Darwin, S.R. Russell, J.M. O'Farrell, M. Fletcher, and B. Wowk (2001). **Rapid (0.5 degrees C/min) minimally invasive induction of hypothermia using cold perfluorochemical lung lavage in dogs.** *Resuscitation* 50(2): 189-204. ISSN: 0300-9572.

Abstract: OBJECTIVE: Demonstrate minimally invasive rapid body core and brain cooling in a large animal model. DESIGN: Prospective controlled animal trial. SETTING: Private research laboratory. SUBJECTS: Adult dogs, anesthetized, mechanically ventilated. INTERVENTIONS: Cyclic lung lavage with FC-75 perfluorochemical (PFC) was administered through a dual-lumen endotracheal system in the new technique of 'gas/liquid ventilation' (GLV). In Trial-I, lavage volume (V-lav) was 19 ml/kg, infused and withdrawn over a cycle period (tc) of 37 s. (effective lavage rate V'-lav=31 ml/kg/min.) Five dogs received cold (approximately 4 degrees C) PFC; two controls received isothermic PFC. In Trial-II, five dogs received GLV at V-lav=8.8 ml/kg, tc=16 s, V'-lav=36 ml/kg/min. MEASUREMENTS AND MAIN RESULTS: Trial-I tympanic temperature change was -3.7+/-0.6 degrees C (SD) at 7.5 min, reaching -7.3+/-0.6 degrees C at 18 min. Heat transfer efficiency was 60%. In Trial-II, efficiency fell to 40%, but heat-exchange dead space (VDtherm) remained constant. Lung/blood thermal equilibration half-time was <8 s. Isothermic GLV caused hypercapnia unless gas ventilation was increased. At necropsy after euthanasia (24 h), modest lung injury was seen. CONCLUSIONS: GLV cooling times are comparable to those for cardiopulmonary bypass. Heat and CO(2) removal can be independently controlled by changing the mix of lavage and gas ventilation. Due to VDtherm of approximately 6 ml/kg in dogs, efficient V-lav is >18 ml/kg. GLV cooling power appears more limited by PFC flows than lavage residence times. Concurrent gas ventilation may mitigate heat-diffusion limitations in liquid

breathing, perhaps via bubble-induced turbulence.
Descriptors: animal model, minimally invasive, rapid body core, brain cooling, hypothermia
.

Hirota, K., Y. Hashimoto, T. Sato, H. Yoshioka, T. Kudo, A. Matsuki, and D.G. Lambert (2001). **Bronchoconstrictive and relaxant effects of lidocaine on the airway in dogs.** *Critical Care Medicine.* 29(5): 1040-4. ISSN: 0090-3493.
Abstract: OBJECTIVE: Intravenous lidocaine commonly is used to treat ventricular arrhythmias and to attenuate reflex airway constriction and intracranial pressure elevation during airway manipulation in intensive care units. There is much controversy as to the actions of lidocaine on the airway, so the aim of this study was to compare, in detail, the actions of lidocaine with those of bupivacaine and procaine on airway caliber and the associated changes in plasma catecholamine concentrations in the dog. DESIGN: Prospective, randomized, controlled experimental in vivo and in vitro study. SETTING: A university research laboratory. SUBJECTS: Mongrel dogs. INTERVENTIONS: In the first experiment, we evaluated the effects of intravenous local anesthetics--lidocaine 0-10 mg/kg (n = 7), bupivacaine 0-2.5 mg/kg (n = 7), or procaine 0-20 mg/kg (n = 7)--on basal airway tone. In second experiment, histamine (10 microg/kg + 500 microg x kg(-1) x hr(-1), n = 6), serotonin (10 microg/kg + 500 microg x kg(-1) x hr(-1), n = 7), and methacholine (0.5 microg/kg + 300 microg x kg(-1) x hr(-1), n = 7) were infused to determine the effects of lidocaine (0-10 mg/kg) on agonist-induced bronchoconstriction. In addition, the actions of lidocaine on vagal nerve stimulation were examined (n = 7). MEASUREMENTS AND MAIN RESULTS: Bronchial cross-sectional area at the third bronchial bifurcation of dogs was monitored continuously through a fiberoptic bronchoscope. In the first experiment, all local anesthetics produced a dose-dependent decrease in basal bronchial cross-sectional area. In the second experiment, lidocaine significantly potentiated histamine and serotonin-induced bronchoconstriction. In contrast, lidocaine antagonized methacholine- and vagal nerve stimulation-induced bronchoconstriction. CONCLUSION: We have clearly demonstrated that lidocaine may produce direct bronchoconstriction and worsen some agonist-induced bronchoconstriction, but it prevents reflex airway constriction. Therefore, we suggest that this agent be used with caution in asthmatics.
Descriptors: animal model, mongrel dogs, intravenous lidocaine, ventricular arrhythmias, reflex airway constriction, intracranial pressure elevation.

Hirota, K., S. Kabara, E. Hashiba, Y. Hashimoto, and A. Matsuki (2002). **Apnea induces bronchoconstriction by vagally mediated reflexes in dogs.** *2000 Annual Meeting of the American Society of Anesthesiologists, San Francisco, CA, USA; October 16-18, 2000,*
Abstract: Introduction: Hypoxia and hypecarbia modulate airway smooth muscle tone1. In addition, respiratory rhythms also change airway tone via pulmonary stretch receptor2. In this study, we determined effect of apnea on bronchial tone in dogs using our bronchoscopic method3. Methods: After approval of our University Animal Care Committee, 14 mongrel dogs anesthetized with pentobarbital (30 mg/kg iv + 2 mg/kg/hr) and pancuronium (0.2 mg/kg/hr) were assigned to two groups: control group (without vagotomy, group C, n=7) and vagotomy group (group V, n=7). The trachea was intubated with an endotracheal tube (ID 7 mm) that has a 2nd lumen for insertion of a superfine fiberoptic bronchoscope

(OD 2.2 mm) to monitor the bronchial cross-sectional area (BCA) continuously as previously reported3. The BCA was measured with MacScope 2.56. In both groups, a respirator was turned off for 5 min to produce apnea. The BCA, arterial oxygen (PaO2) and carbon dioxide tensions (PaCO2) was assessed at before and 1, 2, 3, 4, and 5 min after respirator was tuned off. Changes in BCA are expressed as % of the basal. All data are mean(SEM). Statistical analysis were done by unpaired t-test and repeated measures ANOVA followed by Fisher's PLSD, appropriately. A $p<0.05$ was considered significant. Results: The BCA in group C time-dependently decreased to 99.4(1.1), 88.9(3.8)*, 79.5(4.5)**, 65.2(6.1)** and 57.6(4.7)** at 1, 2, 3, 4 and 5 min after apnea started, respectively, while did not in group V (*: $p<0.05$, **: $p<0.01$ vs group V). Apnea significantly decreased PaO2: 472(17), 445(8), 370(29)**, 282(37)**, 196(43)** and 149(43)**, and increased PaCO2: 41(1), 53(1)**, 58(2)**, 63(2)**, 67(2)** and 71(2)** before and 1, 2, 3, 4 and 5 min after apnea started (N.S between groups). Conclusion: The present study shows that apnea produces bronchoconstriction. In addition, this airway constriction is vagally mediated.
Descriptors: respiratory system, respiration, apnea, respiratory system disease, macscope 2.56, medical equipment, bronchoscopy, experimental surgical techniques, laboratory techniques, endotracheal tube, medical equipment, superfine fiberoptic bronchoscope, medical equipment, vagotomy, experimental surgical techniques, bronchial cross sectional area [bca], bronchial tone, bronchoconstriction, vagally mediated reflexes.

Hsia, C.C.W., R.L.J. Johnson, E.Y. Wu, A.S. Estrera, H. Wagner, and P.D. Wagner (2003). **Reducing lung strain after pneumonectomy impairs oxygen diffusing capacity but not ventilation-perfusion matching.** *Journal of Applied Physiology* 95(4): 1370-1378. ISSN: 8750-7587.
NAL Call Number: 447.8 J825
Abstract: After pneumonectomy (Pnx), mechanical strain on the remaining lung is an important signal for adaptation. To examine how mechanical lung strain alters gas exchange adaptation after Pnx, we replaced the right lung of adult dogs with a custom-shaped inflatable silicone prosthesis. The prosthesis was kept 1) inflated (Inf) to reduce mechanical strain of the remaining lung and maintain the mediastinum in the midline, or 2) deflated (Def) to allow lung strain and mediastinal shift. Gas exchange was studied 4-7 mo later at rest and during treadmill exercise by the multiple inert gas elimination technique while animals breathed 21 and 14% O2 in balanced order. In the Inf group compared with Def group during hypoxic exercise, arterial O2 saturation was lower and alveolar-arterial O2 tension difference higher, whereas O2 diffusing capacity was lower at any given cardiac output. Dispersion of the perfusion distribution was similar between groups at rest and during exercise. Dispersion of the ventilation distribution was lower in the Inf group at rest, associated with a much higher respiratory rate, but rose to similar levels in both groups during hypoxic exercise. Mean pulmonary arterial pressure at a given cardiac output was higher in the Inf group, whereas peak cardiac output was similar between groups. Thus creating lung strain by post-Pnx mediastinal shift primarily enhances diffusive gas exchange with only minor effects on ventilation-perfusion matching, consistent with the generation of additional alveolar-capillary surfaces but not conducting airways and blood vessels.
Descriptors: equipment apparatus devices and instrumentation, respiratory system, pneumonectomy, experimental surgical techniques, laboratory techniques, silicone prosthesis, prosthetic, alveolar arterial oxygen tension difference, arterial oxygen saturation, cardiac

output, gas exchange adaptation, hypoxic exercise, mean pulmonary arterial pressure, oxygen diffusing capacity, respiratory rate.

Hubloue, I., D. Biarent, S. Abdel Kafi, G. Bejjani, C. Melot, R. Naeije, and M. Leeman (2003). **Endothelin receptor blockade in canine oleic acid-induced lung injury.** *Intensive Care Medicine* 29(6): 1003-6. ISSN: 0342-4642.

Abstract: OBJECTIVE: To investigate the effects of endogenous endothelins on pulmonary haemodynamics and gas exchange in oleic acid lung injury. DESIGN: Prospective experimental study in dogs. SETTING: Animal research laboratory in a university teaching hospital. SUBJECTS. Seventeen anaesthetised and ventilated mongrel dogs. INTERVENTIONS: Nine pretreated dogs received an infusion of the endothelin A and B receptor antagonist bosentan (10 mg/kg) started before oleic acid. Eight treated dogs received bosentan started 90 min after oleic acid. Cardiac index (CI) was manipulated by inflating an inferior vena caval balloon or by opening a femoral arterio-venous bypass. MEASUREMENTS AND RESULTS: Pulmonary vascular resistance was defined by measuring the gradient between mean pulmonary artery pressure (MPAP) and occluded PAP (PAOP) at five levels of CI. Intrapulmonary shunt was measured using the inert gas SF(6). Pretreatment with bosentan prevented the oleic acid-induced shift of (MPAP-PAOP)/CI plots to higher pressures, but did not affect the increase in intrapulmonary shunt. Treatment of established oleic acid lung injury with bosentan had no effect. CONCLUSIONS: Pretreatment, but not treatment, with bosentan, in the dose used, blunted the oleic acid-induced increase in pulmonary vascular resistance, suggesting that endothelins contribute to the increase in pulmonary vascular tone in the early stages of oleic acid lung injury.

Descriptors: animal model, lung injury, besentan, oleic acid, pulmonary vascular resistance, endothelins.

Hwang, J.H., Y.S. Kwon, E.H. Kang, W.J. Koh, K.W. Kang, H.C. Kim, M.P. Chung, H. Kim, O.J. Kwon, and G.Y. Suh (2004). **Prone positioning improves oxygenation without adverse hemodynamic effects during partial liquid ventilation in a canine model of acute lung injury**. *Korean Journal of Internal Medicine* 19(4): 237-242. ISSN: 1226-3303.

Abstract: Background : Partial liquid ventilation (PLV) and prone positioning can improve the arterial oxygenation (PaO2) in acute lung injury (ALI). We evaluated the effect of prolonged prone positioning during partial liquid ventilation (PLV) in a canine model of acute lung injury. Methods : Six mongrel dogs (weighing 17.4+/-0.7 kg each) were anesthetized, intubated and mechanically ventilated. After 1 hour of baseline stabilization, the dogs' lungs were instilled with 40 mL/kg perfluorocarbon (PFC). PLV was first performed in the supine position for 1 hour (S1), then in the prone position for 3 hours with hourly measurements (P1, P2, P3), and finally, PLV was performed with the animal turned back to the supine position for 1 hour (S2). Results : After instillation of the PFC, the PaO2 significantly increased from 99.2 +/- 32.6 mmHg at baseline to 198.1 +/- 59.2 mmHg at S1 (p=0.001). When the dogs were turned to the prone position, the PaO2 further increased to 288.3 +/- 80.9 mmHg at P1 (p=0.008 vs. S1): this increase was maintained for 3 hours, but the PaO2 decreased to 129.4 +/- 62.5 mmHg at S2 (p0.001 vs. P3). Similar changes were seen in the shunt fraction. There were no significant differences for the systemic hemodynamic parameters between the prone and supine positions. Conclusion : Prolonged prone positioning during PLV in an

animal model of ALI appears to improve oxygenation without any hemodynamic compromise.

Descriptors: methods and techniques, respiratory system, respiration, acute lung injury, respiratory system disease, therapy, partial liquid ventilation, clinical techniques, therapeutic and prophylactic techniques, prone positioning, oxygenation .

Jahan Parwar, B., D.K. Chhetri, S. Hart, S. Bhuta, and G.S. Berke (2003). **Development of a canine model for recurrent respiratory papillomatosis.** *Annals of Otology Rhinology and Laryngology* 112(12): 1011-1013. ISSN: 0003-4894.

Abstract: A canine model for recurrent respiratory papillomatosis (RRP) was developed with canine oral papillomavirus (COPV) inoculated into the buccal mucosa and supraglottic larynx of 5 beagles. The animals received systemic immunosuppression with daily oral prednisone at doses of 0, 1, 2, 3, and 4 mg/kg. Buccal papillomata developed at 6 weeks in all animals and regressed by 10 weeks in the animals that received 0 and 1 mg/kg. The other animals had continuous growth of their buccal papillomata for 26 weeks. The animal that received 2 mg/kg developed papillomata on the lingual surface of the epiglottis that continued to grow through 26 weeks. Systemic oral prednisone successfully maintained COPV-induced oral and laryngeal papillomata in beagles. Thus, COPV-induced oral and laryngeal papillomata that are prednisone-maintained may have utility as a model for RRP.

Descriptors: oncology, human medicine, medical sciences, otolaryngology, human medicine, medical sciences, pulmonary medicine, human medicine, medical sciences, recurrent respiratory papillomatosis, neoplastic disease, respiratory system disease.

Kafi, S.A., P. Scillia, C. Melot, P.A. Gevenois, A. Pagnamenta, and R. Naeije (2002). **Abnormal pulmonary vascular tone in canine oleic acid lung injury.** *Critical Care Medicine.* 30(7): 1565-9. ISSN: 0090-3493.

Abstract: OBJECTIVE: To characterize the endothelium-dependent and endothelium-independent components of abnormal pulmonary vascular tone in canine oleic acid lung injury. DESIGN: Prospective, interventional study. SETTING: University laboratory. SUBJECTS: Twenty anesthetized mongrel dogs. INTERVENTIONS: Right heart catheterization was performed to measure pulmonary vascular resistance before and after induction of oleic acid lung injury in ten anesthetized and ventilated dogs. Pulmonary and internal mammary artery rings were sampled in these ten dogs with oleic acid injury and in ten anesthetized healthy control dogs. We also studied the responses to acetylcholine, to phenylephrine, and to hypoxia of the intact or endothelium-denuded rings mounted in organ baths. MEASUREMENTS AND MAIN RESULTS: Oleic acid lung injury was associated with an increase in pulmonary vascular resistance from 118 +/- 11 to 245 +/- 47 dyne.sec.cm-5.m-2 and a decrease in the Pao2/Fio2 ratio from 451 +/- 42 to 139 +/- 26 mm Hg (mean +/- se, p <.05 and p <.01, respectively). Acetylcholine-induced relaxation was decreased in the oleic acid pulmonary artery rings compared with the controls (85 +/- 3% vs. 99 +/- 6% of precontraction level, p <.05). Phenylephrine-induced contraction was decreased in denuded oleic acid pulmonary artery rings compared with the controls (81 +/- 8% vs. 102 +/- 10% of contraction to KCl 120 mM, p <.05). In vitro hypoxia induced a small endothelium-dependent contraction followed by an endothelium-independent relaxation. These responses were not different in oleic acid lung artery rings and in controls, except for a decrease in hypoxic

contraction in the oleic acid pulmonary artery rings. In vitro hypoxic pulmonary vasoconstriction and relaxation were, respectively, directly (r =.48) and inversely (r = -.67) correlated with oleic acid-induced increase in pulmonary vascular resistance. There was no correlation between in vitro internal mammary artery reactivity and oleic acid-induced increase in pulmonary vascular resistance. CONCLUSIONS: Oleic acid-induced lung injury slightly impairs pulmonary arterial endothelium-dependent relaxation and endothelium-independent contraction. In vitro hypoxic pulmonary vasoreactivity is related to in vivo oleic acid-induced increase in pulmonary vascular resistance.
Descriptors: animal model, oleic acid, induced lung injury, pulmonary vasoreactivity.

Katzenelson, R., A. Perel, H. Berkenstadt, S. Preisman, S. Kogan, L. Sternik, and E. Segal (2004). **Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water.** *Critical Care Medicine.* 32(7): 1150-4. ISSN: 0090-3493.
Abstract: OBJECTIVE: Pulmonary edema is a severe and often life-threatening condition. The diagnosis of pulmonary edema and its quantification have great clinical significance and yet can be difficult. A new technique based on thermodilution measurement using a single indicator has recently been developed (PiCCO, Pulsion Medical Systems, AG Germany). This method allows the measurement of extravascular lung water and thus can quantify degree of pulmonary edema. The technique has not been compared with a gold standard, gravimetric measurement of extravascular lung water. Therefore, the objective of this study was to determine the ability of extravascular lung water measurement with the PiCCO to reflect the extravascular lung water as measured with a gravimetric technique in a dog model of pulmonary edema. DESIGN: Prospective, randomized animal study. SETTING: A university animal research laboratory. SUBJECTS: Fifteen mongrel dogs (n = 5/group) weighing 20-30 kg. INTERVENTIONS: The dogs were anesthetized and mechanically ventilated. Five dogs served as controls; in five dogs hydrostatic pulmonary edema was induced using inflation of a left atrial balloon combined with fluid administration to maintain a high pulmonary artery occlusion pressure; and in five dogs pulmonary edema was induced by intravenous injection of oleic acid. After a period of stabilization in a state of pulmonary edema, extravascular lung water was measured with the PiCCO monitor. The animals were then killed, and extravascular lung water was measured using a gravimetric technique. MEASUREMENTS AND MAIN RESULTS: There was a very close (r =.967, p <.001) relationship between transpulmonary thermodilution and gravimetric measurements. The measurement with the PiCCO was consistently higher, by 3.01 +/- 1.34 mL/kg, than the gravimetric measurement. CONCLUSIONS: Measurement of extravascular lung water using transpulmonary thermodilution with a single indicator is very closely correlated with gravimetric measurement of lung water in both increased permeability and hydrostatic pulmonary edema.
Descriptors: animal model, induced edema, pulmonary edema, thermodilution measuremnt
.

Khosla, S., S. Muruguppan, E. Gutmark, and R. Scherer (2007). **Vortical flow field during phonation in an excised canine larynx model.** *Annals of Otology, Rhinology, and Laryngology* 116(3): 217-28. ISSN: 0003-4894.
Abstract: OBJECTIVES: To more fully understand the mechanisms of vocal fold vibration

and sound production, we studied the velocity flow fields above the folds. Such velocity fields during phonation have not been reported in the literature. METHODS: Using the particle image velocimetry method for 3 excised canine larynges, we obtained the velocity fields in the mid-membranous coronal plane during different phases of phonation. The velocity field was determined synchronously with the vocal fold motion recorded by high-speed videography. RESULTS: The results show that vortices occur immediately above the vocal folds and that the location and shape of the vortices depend on the phase of the phonation cycle. Consistent vortical structures found included starting vortices, Kelvin-Helmholtz vortices, entrainment vortices, and vortices directly above the folds during the divergent glottal stage. CONCLUSIONS: These vortical structures were consistently found during specific phases of the glottal cycle for 3 canine larynges that significantly varied in size. This consistent behavior suggests that the vortices may be important for both vibration and sound production; however, further study is needed to prove this. The clinical significance of these vortices is discussed.

Descriptors: acoustics, larynx physiology, phonation physiology, dogs, lasers, models, animal, photography, signal processing, computer assisted.

Kling, D.E. and J.J. Schnitzer (2007). **Vitamin A deficiency (VAD), teratogenic, and surgical models of congenital diaphragmatic hernia (CDH).** *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 145c(2): 139-57. ISSN: 1552-4868.

Abstract: Congenital diaphragmatic hernia (CDH) is a congenital malformation that occurs with a frequency of 0.08 to 0.45 per 1,000 births. Children with CDH are born with the abdominal contents herniated through the diaphragm and exhibit an associated pulmonary hypoplasia which is frequently accompanied by severe morbidity and mortality. Although the etiology of CDH is largely unknown, considerable progress has been made in understanding its molecular mechanisms through the usage of genetic, teratogenic, and surgical models. The following review focuses on the teratogenic and surgical models of CDH and the possible molecular mechanisms of nitrofen (a diphenyl ether, formerly used as an herbicide) in both induction of CDH and pulmonary hypoplasia. In addition, the mechanisms of other compounds including several anti-inflammatory agents that have been linked to CDH will be discussed. Furthermore, this review will also explore the importance of vitamin A in lung and diaphragm development and the possible mechanisms of teratogen interference in vitamin A homeostasis. Continued exploration of these models will bring forth a clearer understanding of CDH and its molecular underpinnings, which will ultimately facilitate development of therapeutic strategies. (c) 2007 Wiley-Liss, Inc.

Descriptors: diaphragm embryology, hernia, diaphragmatic embryology, lung embryology, vitamin a physiology, vitamin a deficiency complications, disease models, animal, dogs, hernia, diaphragmatic chemically induced, hernia, diaphragmatic genetics, models, animal, phenyl ethers pharmacology, rabbits, rats, sheep, signal transduction, species specificity, teratogens pharmacology, tretinoin metabolism, vitamin a metabolism.

Krolo, M., A.G. Stucke, E.A.E. Stuth, F.A. Hopp, and E.J. Zuperku (2003). **Responses of prebotzinger complex respiratory neurons to pulmonary afferent inputs in the decerebrate canine model.** *FASEB Journal* 17(4-5): Abstract No. 303.10. ISSN: 0892-6638.

NAL Call Number: QH301.F3

Descriptors: nervous system, neural coordination, respiratory system, respiration, cycle triggered histograms, histology and cytology techniques, laboratory techniques, decerebration, experimental surgical techniques, extracellular single unit recording, phrenic neurogram, electrically induced step vagal input patterns.

Kwon, O.J., G.Y. Suh, M.P. Chung, J. Kim, J. Han, and H. Kim (2003). **Tracheal stenosis depends on the extent of cartilaginous injury in experimental canine model.** *Experimental Lung Research* 29(6): 329-338. ISSN: 0190-2148.
Abstract: To test the hypothesis that the development of tracheal stenosis would depend on the extent of tracheal cartilaginous injury, either 90degree (n=6) or 180degree (n=6) of anterior wall of 4 tracheal rings were cauterized in 12 mongrel dogs using Nd-YAG laser. Beginning at 3 weeks after cauterization, 180degree tracheal injury resulted in life-threatening tracheal stenosis whereas 90degree injury did not. Gross and microscopic examinations showed that after 180degree injury, tracheal stenosis was accompanied by the loss of tracheal cartilage and dense fibrosis. These results indicate that tracheal stenosis depends on the extent of tracheal injury in experimental canine model.
Descriptors: respiratory system, respiration, tracheal cartilaginous injury, connective tissue disease, tracheal stenosis, respiratory system disease, nd yag laser, neodymium yag laser, laboratory equipment, microscopic examination, imaging and microscopy techniques, laboratory techniques.

Lafrentz, J.R., S.E. Brietzke, and E.A. Mair (2003). **Evaluation of palatal snoring surgery in an animal model.** *Otolaryngology Head and Neck Surgery* 129(4): 343-52. ISSN: 0194-5998.
Abstract: OBJECTIVE: We introduce an animal model to reproduce and measure palatal snoring and to assess the effectiveness of cautery-assisted palatal stiffening operation and injection snoreplasty versus a control (no palatal intervention) on treatment of palatal flutter snoring.Study design and setting An anesthetized laboratory canine model uses 2 simultaneous temporary tracheotomies. An inferior tracheotomy is cannulated with an endotracheal tube for ventilation. A superior tracheotomy is cannulated with a tube passed cephalad and seated in the hypopharynx. Negative pressure applied to the upper tube leads to partial collapse of the upper airway with palatal fluttering, and the anesthetized dog snores. Videostroboscopy records palatal flutter frequency before and after surgical intervention. Preoperative and postoperative palatal assessments are made on 15 beagles. RESULTS: Cautery-assisted palatal stiffening operation and injection snoreplasty objectively stiffen the canine soft palate with diminished snoring compared with controls.Conclusion and significance We provide a reproducible animal model to experimentally measure new interventions to treat palatal flutter snoring.
Descriptors: animal model, snoring, intervention, palatal stiffening operation, injection snoreplasty.

Leather, H.A., P. Segers, N. Berends, E. Vandermeersch, and P.F. Wouters (2002). **Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension.** *Critical Care Medicine.* 30(11): 2548-52. ISSN: 0090-3493.
Abstract: OBJECTIVE: Arginine vasopressin is a promising systemic vasopressor in settings such as vasodilatory shock and cardiopulmonary resuscitation. The evidence that arginine

vasopressin may also have a pulmonary vasodilatory effect makes it an attractive drug for the treatment of circulatory shock secondary to right ventricular failure and pulmonary hypertension. In the present study, we evaluated the effects of arginine vasopressin on right ventricular function and ventriculovascular coupling in the setting of moderate acute pulmonary hypertension and compared these effects with those of phenylephrine. DESIGN: Prospective laboratory investigation using an established model of acute pulmonary hypertension. SETTING: University hospital laboratory. SUBJECTS: Seven adult beagle dogs weighing 8-14 kg. INTERVENTIONS: After acute instrumentation to measure right ventricular pressure and volume with the conductance technique and pulmonary artery flow and pressure with high-fidelity transducers, the stable thromboxane analogue U46619 was infused continuously to obtain stable pulmonary hypertension. Phenylephrine and arginine vasopressin were administered consecutively in continuous infusions at doses titrated to achieve a 25% increase in aortic pressure. MEASUREMENTS AND MAIN RESULTS: Phenylephrine and arginine vasopressin both increased total pulmonary vascular resistance and arterial elastance without influencing characteristic impedance. Both drugs decreased cardiac output and stroke volume. Right ventricular hydraulic power output was reduced by arginine vasopressin but not by phenylephrine. Most importantly, arginine vasopressin caused a 31% decrease in right ventricular contractility measured as the slope of the preload recruitable stroke work relationship, whereas contractility was preserved during phenylephrine infusion. CONCLUSIONS: In the present model, arginine vasopressin causes pulmonary vascular constriction and exerts an important negative inotropic effect on the right ventricle. These findings suggest that one should be cautious in the use of arginine vasopressin when right ventricular function is compromised.
Descriptors: beagle dogs, adult, arginine vasopressin, pulmonary vascular resistance, pulmonary hypertension.

Leduc, D., E. Brunko, and A. de Troyer (2001). **Response of the canine internal intercostal muscles to chest wall vibration.** *American Journal of Respiratory and Critical Care Medicine* 163(1): 49-54. ISSN: 1073-449X.
NAL Call Number: RC705 .A4
Abstract: Although high-frequency mechanical vibration of the rib cage reduces dyspnea, its effects on the respiratory muscles are largely unknown. We have previously shown that in anesthetized dogs, vibrating the rib cage during inspiration elicits a marked increase in the inspiratory electromyographic (EMG) activity recorded from the external intercostal muscles but does not affect tidal volume (VT). In the present studies, we have tested the hypothesis that the maintenance of VT results from the concomitant contraction of the internal interosseous (expiratory) intercostals. When the rib cage was vibrated (40 Hz) during hyperventilation-induced apnea, a prominent activity was recorded from the external intercostals but no activity was recorded from the internal intercostals, including when the muscles were lengthened by passive inflation. The internal intercostals remained also silent when vibration was applied during spontaneous inspiration, and the phasic expiratory EMG activity recorded from them was unaltered when vibration was applied during expiration. Thus, the internal interosseous intercostals in dogs are much less sensitive to vibration than the external intercostals, and they do not interfere with the action of these latter during rib cage vibration. This lack of sensitivity might be the result of a reflex inhibition of the muscle spindle

afferents by afferents from external intercostal muscle spindles.
Descriptors: mechanical vibration, rib cage, dyspnea, EMG, passive inflation.

Leduc, D. and A. de Troyer (2003). **Mechanical effect of muscle spindles in the canine external intercostal muscles.** *Journal of Physiology* 548(Pt 1): 297-305. ISSN: 0022-3751.
NAL Call Number: 447.8 J82
Abstract: High-frequency mechanical vibration of the ribcage increases afferent activity from external intercostal muscle spindles, but the effect of this procedure on the mechanical behaviour of the respiratory system is unknown. In the present study, we have measured the changes in external intercostal muscle length and the craniocaudal displacement of the ribs during ribcage vibration (40 Hz) in anaesthetized dogs. With vibration, external intercostal inspiratory activity increased by approximately 50 %, but the respiratory changes in muscle length and rib displacement were unaltered. A similar response was obtained after the muscles in the caudal segments of the ribcage were sectioned and the caudally oriented force exerted by these muscles on the rib was removed, thus suggesting that activation of external intercostal muscle spindles by vibration generates little tension. Prompted by this observation, we also examined the role played by the external intercostal muscle spindles in determining the respiratory displacement of the ribs during breathing against high inspiratory airflow resistances. Although resistances consistently elicited prominent reflex increases in external intercostal inspiratory activity, the normal inspiratory cranial displacement of the ribs was reversed into an inspiratory caudal displacement. Also, this caudal rib displacement was essentially unchanged after section of the external intercostal muscles, whereas it was clearly enhanced after denervation of the parasternal intercostals. These findings indicate that stretch reflexes in external intercostal muscles confer insufficient tension on the muscles to significantly modify the mechanical behaviour of the respiratory system.
Descriptors: high frequency mechanical vibration, ribcage, intercostal muscle spindles, mechanical behavior, respiratory system.

Lim, C.M., S.S. Lee, J.S. Lee, Y. Koh, T.S. Shim, S.D. Lee, W.S. Kim, D.S. Kim, and W.D. Kim (2003). **Morphometric effects of the recruitment maneuver on saline-lavaged canine lungs: a computed tomographic analysis.** *Anesthesiology (Hagerstown)* 99(1): 71-80. ISSN: 0003-3022.
Abstract: Background: In the face of widespread use of lung-protective, low-volume ventilation in patients with acute lung injury, interest in the recruitment maneuver (RM) is growing. Little is known about lung-morphometric effects of the RM as compared with positive end-expiratory pressure (PEEP) titration (PT) without the RM. Methods: RM was defined as a stepwise change in PEEP from baseline to 10, 20, 30, and 20 cm H2O every 30 s, after which PEEP was reset at the lower inflection point + 2 cm H2O. For PT, PEEP was simply increased from baseline to the lower inflection point + 2 cm H2O. Both maneuvers were performed in 10 lung-lavaged dogs. Computed tomography of the lung was performed before and 30 s and 30 min after the maneuver. Results: Thirty seconds after the maneuver, the decrease in the amount of nonaerated plus poorly aerated lung was greater and decreases in Hounsfield units in the caudal and dorsal lung regions were greater with the RM than with the PT. The hyperaerated lung volume after the RM tended to be greater than that after the PT. At 30 s and 30 min after the maneuver, gas plus tissue volume, gas-only volume,

and gas-tissue ratio of the lung were greater with the RM than with the PT. At both time points after the maneuver, the coefficient of variation of regional Hounsfield units, an index of regional heterogeneity of aeration, was lower with the RM than with the PT. Conclusions: Compared with PT, the RM resulted in a greater lung volume, better aeration of the most dependent lung, and less regional heterogeneity of aeration. However, the RM tended to induce a greater increase in hyperaerated lung volume than did the PT.
Descriptors: methods and techniques, respiratory system, respiration, computed tomographic analysis, computed tomography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, positive end expiratory pressure titration, recruitment maneuver, clinical techniques, aeration, regional heterogeneity, gas plus tissue volume, gas only volume, gas tissue ratio, hyperaerated lung volume, morphometric effects, regional hounsfield units, coefficient of variation, saline lavaged.

Lin, V.W., I. Hsiao, X. Deng, Y.S. Lee, and S. Sasse (2004). **Functional magnetic ventilation in dogs.** *Archives of Physical Medicine and Rehabilitation* 85(9): 1493-8. ISSN: 0003-9993.
Abstract: OBJECTIVE: To investigate the efficacy of the magnetic stimulation of inspiratory muscles as an alternative to mechanical ventilation and functional electric stimulation. DESIGN: A prospective before-after trial. SETTING: Functional magnetic stimulation laboratory in a Veterans Administration health care system. ANIMALS: Six male mongrel dogs, each weighing between 25 and 35 kg. INTERVENTIONS: Commercially available magnetic stimulators with a round magnetic coil were used. The center of the magnetic coil was placed posteriorly over the C5-7 vertebrae of the spinal cord transected dogs. Magnetic stimulation parameters were set at 80% intensity, 20 Hz, and a 1.2-second on and 3.8-second off pulse train. MAIN OUTCOME MEASURES: The major outcomes were changes in tidal volume (VT), tracheal pressure (Ptr), and arterial partial pressure of carbon dioxide (PaCO2) and oxygen sustained by magnetic stimulation over time. RESULTS: The average Vt and Ptr produced during functional magnetic ventilation (FMV) were.47+/-.07 L and -4.7+/-.51 cmH2O, respectively. Blood gas data showed that PaCO2 increased from a baseline of 33 to 75 mmHg, whereas pH decreased from 7.33 to 6.99 at the end of the 1-hour FMV period. CONCLUSIONS: FMV was achieved for 2 hours in dogs with C2 spinal cord transection. Additional refinements in magnetic stimulation are needed to improve ventilation in animals.
Descriptors: animal model, mongrel dogs, spinal cord transection, magnetic stimulatior, alternatives, mechanical ventilation.

Loer, S.A., L.A. Schwarte, M.A. Pakulla, O. Picker, and T.W. Scheeren (2003). **Partial liquid ventilation: effects of positive end-expiratory pressure on perfluorocarbon evaporation from the lungs of anesthetized dogs.** *Intensive Care Medicine* 29(3): 467-70. ISSN: 0342-4642.
Abstract: OBJECTIVE: Perfluorocarbons are eliminated during partial liquid ventilation mainly by evaporation via the airways. We examined whether this is affected by the level of end-expiratory airway pressure. DESIGN AND SETTING: Observational cohort animal study in the animal laboratory of a university hospital. SUBJECTS: Five foxhound dogs. INTERVENTIONS: The anesthetized dogs underwent partial liquid ventilation (5 ml/kg perfluorocarbon) at constant respiratory rate (17+/-1 breaths/min) and tidal volume (10 ml/kg). The level of end-expiratory airway pressure was varied repeatedly between 0, 5, and 10 cmH(2)O every 25 min. MEASUREMENTS AND RESULTS: Expired gas was collected

in reservoirs to determine evaporative perfluorocarbon loss gravimetrically. Any increase in end-expiratory airway pressure increased while any decrease in end-expiratory airway pressure reduced evaporative perfluorocarbon loss. Mean initial elimination at an end-expiratory airway pressure of 5 cmH(2)O was 19.6+/-3.8 microl/kg per minute; this decreased by 28% at an end-expiratory airway pressure of 0 cmH(2)O and increased by 46% at an end-expiratory airway pressure of 10 cmH(2)O. At equal levels of end-expiratory airway pressure evaporation decreased linearly over time. CONCLUSIONS: Our results suggest that the level of end

Descriptors: animal model, foxhound dogs, perfluorocarbons, partial liquid ventilation.

Mcverry, B.J., X. Peng, P.M. Hassoun, S. Sammani, B.A. Simon, and J.G.N. Garcia (2004). **Sphingosine 1-phosphate reduces vascular leak in murine and canine models of acute lung injury**. *American Journal of Respiratory and Critical Care Medicine* 170(9): 987-993. ISSN: 1073-449X.

NAL Call Number: RC705 .A4

Abstract: Excessive mechanical stress is a key component of ventilator-associated lung injury, resulting in profound vascular leak and an intense inflammatory response. To extend our in vitro observations concerning the barrier-protective effects of the lipid growth factor sphingosine 1-phosphate (Sph 1-P), we assessed the ability of Sph 1-P to prevent regional pulmonary edema accumulation in clinically relevant rodent and canine models of acute lung injury induced by combined intrabronchial endotoxin administration and high tidal volume mechanical ventilation. Intravenously delivered Sph 1-P significantly attenuated both alveolar and vascular barrier dysfunction while significantly reducing shunt formation associated with lung injury. Whole lung computed tomographic image analysis demonstrated the capability of Sph 1-P to abrogate significantly the accumulation of extravascular lung water evoked by 6-hour exposure to endotoxin. Axial density profiles and vertical density gradients localized the Sph 1-P response to transitional zones between aerated and consolidated lung regions. Together, these results indicate that Sph 1-P represents a novel therapeutic intervention for the prevention of pulmonary edema related to inflammatory injury and increased vascular permeability.

Descriptors: pharmacology, respiratory system, respiration, lung injury, injury, respiratory system disease, pulmonary edema, respiratory system disease, drug therapy, pathology, prevention and control, mechanical ventilation, clinical techniques, therapeutic and prophylactic techniques, tomography, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, mechanical stress.

Miao, C.H., B. Sun, H. Jiang, Z.G. Xue, and R. Lindwall (2002). **Pharmacodynamics and pharmacokinetics of inhaled nitric oxide in dogs with septic acute respiratory distress syndrome.** *Acta Pharmacologica Sinica* 23(3): 278-84. ISSN: 1671-4083.

Abstract: AIM: To evaluate pharmacodynamics and pharmacokinetics of inhaled nitric oxide (iNO) in dogs with acute respiratory distress syndrome (ARDS). METHODS: ARDS, induced after iv injection of endotoxin, was evidenced by reduction of paO2/FiO2 from (62.5 +/- 2.8) to (26 +/- 4) kPa and dynamic lung compliance (Cdyn) from (14.8 +/- 0.7) to (8.6 +/- 0.6) mL.kPa-1 . kg-1, increase of dead space (VD/VT) from (0.14 +/- 0.06) to (0.58 +/- 0.05), intrapulmonary shunting (Qs/Qt) from 4.7 % +/- 1.7 % to 39 % +/- 7 %,

and pulmonary vascular resistance index (PVRI) from (16 +/- 4) to (51 +/- 8) kPa.s.L-1 . m-2 (all P < 0.05), along with severe intrapulmonary neutrophil recruitment and peripheral neutropenia. The animals were then treated as either a control or an NO group (n = 6 each, iNO 0.4 - 3.2 micromol/L) for another 10 h. RESULTS: More survival was found in NO group (4/6 vs 0/6, P < 0.05). iNO at 0.8, 1.6, and 3.2 micromol/L (20, 40, and 80 ppm) resulted in > 40 % increase of paO2/FiO2 and Cdyn, a reduction of VD/VT to 0.32, Qs/Qt to < 25 %, and PVRI by > 50 % (30.8 kPa . s . L-1 . m-2) compared to the control. Optimal iNO dose was around 0.8 micromol/L as higher methemoglobin (MetHb, > 3 %) was found at higher NO. iNO had no adverse effects on surfactant phospholipids and lung fluid balance, but attenuated expression of tumor necrosis factor alpha,beta2 integrin CD11b, and interleukin-8 mRNA in the lungs by 22 %, 44 %, and 25 %, respectively (P < 0.05). CONCLUSION: Pharmacodynamics of iNO in this model was related to improvement in gas exchange, Cdyn, PVRI, and suppression of proinflammatory cytokine expression in the lungs, and its adverse effect was mainly confined to MetHb at higher NO dose.
Descriptors: pharmacodynamics, pharmacokinetics, inhaled nitric oxide (iNO), acute respiratory distress syndrome, intrapulmonary neutrophil recruitment, peripheral neutropenia, surfactant phospholipids, lung fluid balance.

Morris, T.A., J.J. Marsh, P.G. Chiles, R.G. Konopka, C.A. Pedersen, P.F. Schmidt, and M. Gerometta (2004). **Single photon emission computed tomography of pulmonary emboli and venous thrombi using anti-d-dimer**. *American Journal of Respiratory and Critical Care Medicine* 169(9): 987-993. ISSN: 1073-449X.
NAL Call Number: RC705 .A4
Abstract: Previous attempts to diagnose thromboemboli using radiolabeled antibodies and nuclear medicine imaging have been disappointing. We present the results of experiments with intravenous technetium-99m-labeled deimmunized antifibrin Fab' fragments to diagnose thromboemboli using single photon emission computed tomography (SPECT), a highly sensitive scintigraphic imaging technique. Pulmonary emboli (PEs) and lower extremity deep vein thrombi (DVTs) were formed in five dogs, then technetium-99m-labeled Fab' (dollar sign 400 mg, dollar sign 260 MBq) were injected via forelimb veins. Thoracic and lower extremity SPECT scans were performed at 2-hour intervals after antibody infusion to visualize the thromboemboli. Four hours after antibody infusion, all PEs and DVTs of mass 0.4g or greater were clearly visualized on SPECT scans as 'hot spots' within the lungs and legs, respectively. PEs (0.48 +/- 0.09 g) were intensely radiolabeled, yielding clot/blood radioactivity ratios of 22.8 +/- 5.6. DVTs (0.45 +/- 0.31 g) also had high clot/blood ratios (11.7 +/- 2.6). Infusion of these radiolabeled antibody fragments, combined with SPECT, produces clear images of PEs and DVTs within a clinically feasible time frame. The technique reliably identified even peripheral thromboemboli of relatively small size, which are difficult to diagnose with currently available imaging techniques, and may enable imaging of PEs, DVTs, or both in the same patient.
Descriptors: cardiovascular medicine, human medicine, medical sciences, pulmonary medicine, human medicine, radiology, medical sciences, deep vein thrombosis, vascular disease, pulmonary emboli, respiratory system disease, venous thrombi, vascular disease, venous thromboembolism, single photon emission computed tomography, spect, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques.

Nair, B. and A.R. Elmore (2003). **Final report on the safety assessment of sodium sulfite, potassium sulfite, ammonium sulfite, sodium bisulfite, ammonium bisulfite, sodium metabisulfite and potassium metabisulfite.** *International Journal of Toxicology* 22(Supplement 2): 63-88. ISSN: 1091-5818.

NAL Call Number: RA1190.J61

Abstract: Sodium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Potassium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are inorganic salts that function as reducing agents in cosmetic formulations. All except Sodium Metabisulfite also function as hair-waving/straightening agents. In addition, Sodium Sulfite, Potassium Sulfite, Sodium Bisulfite, and Sodium Metabisulfite function as antioxidants. Although Ammonium Sulfite is not in current use, the others are widely used in hair care products. Sulfites that enter mammals via ingestion, inhalation, or injection are metabolized by sulfite oxidase to sulfate. In oral-dose animal toxicity studies, hyperplastic changes in the gastric mucosa were the most common findings at high doses. Ammonium Sulfite aerosol had an acute LC50 of >400 mg/m3 in guinea pigs. A single exposure to low concentrations of a Sodium Sulfite fine aerosol produced dose-related changes in the lung capacity parameters of guinea pigs. A 3-day exposure of rats to a Sodium Sulfite fine aerosol produced mild pulmonary edema and irritation of the tracheal epithelium. Severe epithelial changes were observed in dogs exposed for 290 days to 1 mg/m3 of a Sodium Metabisulfite fine aerosol. These fine aerosols contained fine respirable particle sizes that are not found in cosmetic aerosols or pump sprays. None of the cosmetic product types, however, in which these ingredients are used are aerosolized. Sodium Bisulfite (tested at 38%) and Sodium Metabisulfite (undiluted) were not irritants to rabbits following occlusive exposures. Sodium Metabisulfite (tested at 50%) was irritating to guinea pigs following repeated exposure. In rats, Sodium Sulfite heptahydrate at large doses (up to 3.3 g/kg) produced fetal toxicity but not teratogenicity. Sodium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite were not teratogenic for mice, rats, hamsters, or rabbits at doses up to 160 mg/kg. Generally, Sodium Sulfite, Sodium Metabisulfite, and Potassium Metabisulfite were negative in mutagenicity studies. Sodium Bisulfite produced both positive and negative results. Clinical oral and ocular-exposure studies reported no adverse effects. Sodium Sulfite was not irritating or sensitizing in clinical tests. These ingredients, however, may produce positive reactions in dermatologic patients under patch test. In evaluating the positive genotoxicity data found with Sodium Bisulfite, the equilibrium chemistry of sulfurous acid, sulfur dioxide, bisulfite, sulfite, and metabisulfite was considered. This information, however, suggests that some bisulfite may have been present in genotoxicity tests involving the other ingredients and vice versa. On that basis, the genotoxicity data did not give a clear, consistent picture. In cosmetics, however, the bisulfite form is used at very low concentrations (0.03% to 0.7%) in most products except wave sets. In wave sets, the pH ranges from 8 to 9 where the sulfite form would predominate. Skin penetration would be low due to the highly charged nature of these particles and any sulfite that did penetrate would be converted to sulfate by the enzyme sulfate oxidase. As used in cosmetics, therefore, these ingredients would not present a genotoxicity risk. The Cosmetic Ingredient Review Expert Panel concluded that Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are safe as used in cosmetic formulations.

Descriptors: cosmetics, toxicology, pulmonary edema, respiratory system disease, oral dose

animal toxicity test, laboratory techniques, genotoxicity data, lung capacity parameters, pH, skin penetration.

Ochs, M., H. Fehrenbach, and J. Richter (2004). **Occurence of lipid bodies in canine type ii pneumocytes during hypothermic lung ischemia**. *Anatomical Record* 277A(2): 287-297. ISSN: 0003-276X.
NAL Call Number: QL801 .A53
Descriptors: biochemistry and molecular biophysics, respiratory system, respiration, cardiac arrest, heart disease, hypothermic lung ischemia, respiratory system disease, vascular disease, pathology, energy filtering transmission, electron microscopy, imaging, microscopy techniques, laboratory techniques, stereology, laboratory techniques, alveolar epithelial regeneration.

Olmos Zuniga, J.R., C. Hernandez Jimenez, E. Diaz Martinez, R. Jasso Victoria, A. Sotres Vega, M.O. Gaxiola Gaxiola, J. Villalba Caloca, M. Baltazares Lipp, P. Santillan Doherty, and J.A. Santibanez Salgado (2007). **Wound healing modulators in a tracheoplasty canine model.** *Journal of Investigative Surgery the Official Journal of the Academy of Surgical Research* 20(6): 333-8. ISSN: 0894-1939.
Abstract: Postsurgical tracheal stenosis results from fibrosis formation due to ischemia. There are healing modulators, hyaluronic acid (HA) and collagen polyvinylpyrrolidone (CPVP), which reduce collagen fibers formation. Thus we can hypothesize that the topical application of one of these modulators can diminish postsurgical tracheal scarring and stenosis. The aim of this work was to evaluate the macroscopic, microscopic, and biochemical changes of tracheal healing after the application of HA or CPVP in a canine tracheoplasty model. The study design was prospective experimental investigation in a canine model. Eighteen mongrel dogs underwent three cervical tracheal rings resection and end-to-end anastomosis. They were randomized into three groups according to treatment: group I (control group) (n = 6), topical application of saline solution on tracheal anastomosis; group II (n = 6), topical application of 15 microg HA on tracheal anastomosis; and group III (n = 6), topical application of 2.5 mg CPVP on tracheal anastomosis. They were evaluated clinical, radiological and tracheoscopically during 4 weeks. They were euthanized at the end of the study time. Macroscopic, microscopic, and biochemical changes of tracheal anastomosis healing were analyzed. Collagen formation was quantified by the Woessner method. All the animals survived the surgical procedure and study period. Macroscopic, radiologic, and endoscopic studies showed that animals in group I developed tracheal stenosis, inflammation, and firm fibrous tissue formation, and histological studies also showed severe inflammatory reaction and fibrosis formation. Groups II (HA) and III (CPVP) showed well-organized thin collagen fibers with minimal inflammatory response. Biochemical evaluation revealed a higher collagen concentration in group I animals (analysis of variance [ANOVA] $p < .05$ and Tukey $p < .01$). Thus, hyaluronic acid or collagen polyvinylpyrrolidone administered after tracheal anastomosis diminished the degree of stenosis and inflammatory reaction. Both modulators improved tracheal healing.
Descriptors: collagen pharmacology, hyaluronic acid pharmacology, povidone pharmacology, trachea surgery, wound healing drug effects, dogs, fibrosis, models, animal, postoperative complications etiology, trachea pathology, tracheal stenosis etiology.

Omori, K., T. Nakamura, S. Kanemaru, H. Kojima, A. Magrufov, Y. Hiratsuka, and Y. Shimizu (2004). **Cricoid regeneration using in situ tissue engineering in canine larynx for the treatment of subglottic stenosis**. *Annals of Otology Rhinology and Laryngology* 113(8): 623-627. ISSN: 0003-4894.

Abstract: The purpose of the present study was to evaluate the efficacy of cricoid regeneration via in situ tissue engineering in a canine larynx for the treatment of subglottic stenosis. As the tissue scaffold, a Marlex mesh tube coated by collagen sponge was used for a rigid airway framework and for tissue regrowth around the tube. On 5 dogs, the larynx was exposed and the anterior third of the cricoid cartilage was resected. The tube was anastomosed to the lower edge of the thyroid cartilage and to the first tracheal cartilage. By postoperative endoscopic examination at 3 to 7 months, no airway obstruction was observed in any of the dogs. There was granulation tissue in 2 dogs and slight mesh exposure in I dog, but they were asymptomatic. Confluent regeneration of the epithelium over the scaffold and good incorporation of the scaffold mesh into the host tissue were observed after surgery.

Descriptors: bioprocess engineering, respiratory system, respiration, subglottic stenosis, respiratory system disease, diagnosis, therapy, endoscopy, diagnostic techniques, laboratory techniques.

Pagnamenta, A., P. Fesler, A. Vandinivit, S. Brimioulle, and R. Naeije (2003). **Pulmonary vascular effects of dobutamine in experimental pulmonary hypertension.** *Critical Care Medicine.* 31(4): 1140-6. ISSN: 0090-3493.

Abstract: OBJECTIVE: To characterize the dose-related effects of dobutamine on pulmonary vascular tone and associated changes in right ventricular afterload in canine microembolic lung injury .DESIGN: Prospective, interventional study. SETTING: University laboratory. SUBJECTS: Ten anesthetized and ventilated dogs. INTERVENTIONS: Right heart catheterization for the measurement of pulmonary vascular resistance by multipoint mean pulmonary artery pressure (Ppa)/cardiac output (Q) plots, partitioning of pulmonary vascular resistance by the occlusion method, and determination of pulmonary arterial input impedance from spectral analysis of Ppa and Q waves, in ten anesthetized and ventilated dogs, before and after induction of acute microembolic lung injury, and without or with 5, 10, 15, and 20 microg.kg(-1).min(-1) dobutamine. MEASUREMENTS AND MAIN RESULTS: Microembolic pulmonary hypertension was associated with a shift of Ppa/Q plots to higher pressures, a slight decrease in the arterial component of pulmonary vascular resistance, a decrease in characteristic impedance, and an increase in the pulsatile component of right ventricular hydraulic load. At baseline, dobutamine had no effect on Ppa/Q plots at 5 and 10 microg.kg(-1).min(-1) but increased Ppa at 15 and 20 microg.kg(-1).min(-1). In microembolic pulmonary hypertension, the only effect of dobutamine on Ppa/Q plots was a decrease in Ppa at 20 microg.kg(-1).min(-1). Dobutamine had no effect on the partitioning of pulmonary vascular resistance or on pulmonary arterial input impedance spectrum. CONCLUSIONS: Dobutamine at doses up to 10 microg.kg(-1).min(-1) has no flow-independent effect on the normal or the acutely hypertensive pulmonary circulation. Higher doses may be constricting or dilating depending on preexisting tone.

Descriptors: lung injury, animal model, ventilated dogs, dose-related effects, dobutamine, pulmonary vascular tone, pulmonary artery pressure.

Park, C.K., K.S. Park, S.H. Jheon, K.Y. Kwon, Y.J. Jeon, and H.C. Kim (2003). **Lung preservation study by canine sequential bilateral single lung transplantation model.** *Transplantation Proceedings* 35(1): 453-455. ISSN: 0041-1345.
NAL Call Number: RD120.7.T68
Descriptors: methods and techniques, respiratory system, respiration, lung edema, respiratory system disease, bilateral single lung transplantation, clinical techniques, therapeutic and prophylactic techniques, arterial oxygen tension, lung preservation study, pulmonary arterial pressure, pulmonary vascular resistance, total ischemic time.

Pellett, A.A., K.C. Lord, M.S. Champagne, B.P. deBoisblanc, R.W. Johnson, and M.G. Levitzky (2002). **Pulmonary capillary pressure during acute lung injury in dogs.** *Critical Care Medicine* 30(2): 403-9. ISSN: 0090-3493.
Abstract: OBJECTIVES: To measure pulmonary capillary pressure and pulmonary artery occlusion pressures both during control conditions and during acute lung injury and to evaluate the effects of inotropic therapy and volume loading on these measurements after lung injury. DESIGN: Prospective, randomized, controlled laboratory trial. SETTING: University research laboratory. SUBJECTS: Eighteen heartworm-free mongrel dogs. INTERVENTIONS: Dogs were anesthetized (sodium pentobarbital, 30 mg/kg intravenously), intubated, and mechanically ventilated. A femoral artery and vein and the right external jugular vein were cannulated. After a median sternotomy, two pulmonary artery catheters were inserted via the jugular vein into the left and right lower lobar pulmonary arteries. Oleic acid (0.03 mL/kg) was administered to all dogs via the left pulmonary artery catheter, whereas the right lower lobe served as control. A baseline group of dogs received no further interventions, whereas two additional groups were given dobutamine (30-60 microg x kg(-1) x min(-1)intravenously) or saline boluses (1-2 L) before measurements were obtained after oleic acid lung injury. MEASUREMENTS AND MAIN RESULTS: Capillary pressure was estimated in both lower lung lobes by using the pulmonary artery occlusion method. Pulmonary capillary and pulmonary artery occlusion pressures were measured before and 2 hrs after oleic acid administration. Left lower lobar capillary pressure increased in all three groups, as did the difference between capillary pressure and pulmonary artery occlusion pressure. Capillary pressure in the control right lower lobe increased significantly only in the saline-loaded dogs, whereas the difference between the right-sided capillary and occlusion pressures increased only in the dogs given dobutamine. CONCLUSIONS: Oleic acid lung injury increases pulmonary capillary pressure independent of pulmonary artery occlusion pressure. The gradient between the two pressures was not significantly affected by volume loading or dobutamine infusion.
Descriptors: animal model, lung injury, pulmonary capillary pressure, pulmonary artery occlusion pressures, volume loading, dobutamine infusion.

Sander, M., K.L.K. Welling, J.B. Ravn, B. Boberg, and O. Amtorp (2003). **Endogenous no does not regulate baseline pulmonary pressure, but reduces acute pulmonary hypertension in dogs.** *Acta Physiologica Scandinavica* 178(3): 269-277. ISSN: 0001-6772.
NAL Call Number: QP1.A2
Abstract: It has remained unclear whether endogenous production of nitric oxide (NO) plays an important role in the regulation of physiologically normal pulmonary pressures.

Severe alveolar hypoxia is accompanied by decreased pulmonary NO production, which could contribute to the development of hypoxic pulmonary hypertension. On the other hand, pharmacological NO inhibition further augments this hypertensive response. Aims: The aims of the present study were to test: (a) whether NO contributes importantly in the maintenance of baseline pulmonary pressure; and (b) to which degree NO is involved in the pulmonary haemodynamic adjustments to alveolar hypoxia. Methods: In anaesthetized dogs (n=37), the systemic and pulmonary haemodynamic effects of the NO synthase inhibitor, Nomega-nitro-L-arginine methyl ester (L-NAME, 20 mg kg-1) and substrate, L-arginine (200-500 mg kg-1), were determined at baseline and during alveolar hypoxia. Constant blood flows were accomplished by biventricular bypass, and systemic normoxaemia was maintained by extracorporeal oxygenation. Results: The primary findings were: (a) L-NAME failed to increase baseline mean pulmonary arterial pressure (10.1+-0.7 vs. 10.5+-0.5 mmHg, P=ns), despite effective NO synthase inhibition as evidenced by robust increases in systemic arterial pressures; (b) L-NAME augmented the pulmonary hypertensive response to alveolar hypoxia (10.2+-0.7 to 19.5+-1.7 with L-NAME vs. 9.9+-1.1 to 15.5+-1.0 mmHg without L-NAME, P<0.05); and (c) L-arginine failed to decrease baseline or elevated pulmonary pressures. Instead, prolonged L-arginine caused increases in pulmonary pressure. Conclusion: These findings suggest that NO plays no significant role in the tonic physiological control of pulmonary pressure, but endogenous NO becomes an important vasodilatory modulator during elevated pulmonary pressure.

Descriptors: cardiovascular system, transport and circulation, respiratory system, respiration, acute pulmonary hypertension, vascular disease, alveolar hypoxia, respiratory system disease, baseline pulmonary pressure.

Satoh, M., P.R. Eastwood, C.A. Smith, and J.A. Dempsey (2001). **Nonchemical elimination of inspiratory motor output via mechanical ventilation in sleep.** *American Journal of Respiratory and Critical Care Medicine* 163(6): 1356-64. ISSN: 1073-449X.

NAL Call Number: RC705 .A4

Abstract: In six dogs studied in nonrapid eye movement (NREM) sleep, we found that the frequency, volume, and timing of application of mechanical ventilator breaths had marked and sustained inhibitory effects on diaphragm electromyogram (EMG(di)). Single ventilator breaths of tidal volume (VT) 75-200% of control caused apnea (up to three times eupneic expiratory time [TE]) when applied during the initial 25-65% of expiratory time. When continuous controlled mechanical ventilation (CMV) was applied with ventilator frequency increased as little as 1 cycle/min > eupnea and Pa(CO(2)) and VT maintained at near eupneic control levels, EMG(di) was silenced and triangularis sterni EMG (EMG(ts)) became tonic within 2 to 5 ventilator cycles. On cessation of normocapnic CMV, apnea ensued with TE ranging from 1.2 to five times eupneic TE. The spontaneous VT and EMG(di) determined immediately after these prolonged apneas were also markedly reduced in amplitude. The larger the VT applied during the isocapnic CMV (120-200% of eupnea) and the longer the duration of the CMV (3-90 s), the longer the duration of the postventilator apnea. Significant postventilator apneas and postapneic hypoventilation also occurred even when end-tidal CO(2) pressure (PET(CO(2))) was raised 3-5 mm Hg > eupnea (and 7-10 mm Hg > normal apneic threshold) throughout CMV trials at raised frequency and VT. Our findings demonstrate that the increased frequency of CMV was critical to the

elimination of inspiratory motor output and the onset of tonic expiratory muscle activity; furthermore, once EMG(di) was silenced, the tidal volume and duration of the passive mechanical ventilation determined the magnitude of the short-term inhibition of inspiratory motor output after cessation of CMV.
Descriptors: nonrapid eye movement (NREM) sleep, mechanical ventilator breaths, diaphragm electromyogram, ventilator breaths .

Schweitzer, C.E., J.L. Johnson, S.G. Vincent, and J.T. Fisher (2003). **Static and dynamic behavior of neonatal canine slowly adapting receptors.** *FASEB Journal* 17(4-5): Abstract No. 558.2. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cell biology, development, respiratory system, respiration, breathing control, neonates, transpulmonary pressure.

Suga, K., Y. Yuan, N. Ogasawara, T. Tsukuda, and N. Matsunaga (2003). **Altered clearance of gadolinium diethylenetriaminepentaacetic acid aerosol from bleomycin-injured dog lungs: initial observations.** *American Journal of Respiratory and Critical Care Medicine* 167(12): 1704-1710. ISSN: 1073-449X.
NAL Call Number: RC705 .A4
Abstract: To characterize altered alveolar transfer to solute in bleomycin (BLM)-injured lungs, eight dogs underwent a gadolinium diethylenetriaminepentaacetic acid aerosol (Gd-AS) magnetic resonance imaging study before and on Days 7 and 40 after tracheal instillation of BLM (0.75 mg) in the left lungs. Consecutive fast-gradient echo magnetic resonance imaging was acquired during and after spontaneous inhalation of 200-mM Gd-AS. The slope (Kep) and clearance half-time (T1/2) of logarithmic regression lines for clearance curves were estimated. Histology on Day 40 was compared with that on Day 7 in another three dogs. On Days 7 and 40, Gd-AS deposition was heterogeneously reduced in the affected lungs. On Day 7 with multifocal intraalveolar exudative changes, Kep in affected areas was significantly increased compared with baseline (2.5X10-3 minutes-1+-0.3 versus 1.7X10-3 minutes-1+-0.2, p<0.0001), with significant decrease in T1/2 (121.6+-19.7 minutes vs. 170.4+-15.8 minutes, p<0.001). However, on Day 40 with multifocal interstitial fibrosis, Kep and T1/2 were recovered toward baseline. BLM-injured lungs can be characterized by accelerated Gd-AS clearance during the acute exudative phase and their recovery during the chronic fibrotic phase. This technique is acceptable for monitoring alveolar transfer changes in BLM-injured lungs.
Descriptors: biochemistry and molecular biophysics, respiratory system, respiration, lung injury, injury, respiratory system disease, magnetic resonance imaging, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, initial observations.

Sugita, M., P. Ferraro, A. Dagenais, M.E. Clermont, P. Barbry, R.P. Michel, and Y. Berthiaume (2003). **Alveolar liquid clearance and sodium channel expression are decreased in transplanted canine lungs.** *American Journal of Respiratory and Critical Care Medicine* 167(10): 1440-1450. ISSN: 1073-449X.
NAL Call Number: RC705 .A4

Abstract: To determine the impact of transplantation-associated injury on the clearance mechanisms of pulmonary edema, we created a canine single lung transplant model. After 3 hours of preservation and 4 hours of reperfusion, right native lungs and left transplanted lungs were used to measure alveolar liquid clearance (ALC) in ex vivo liquid-filled lung preparations. We also examined the role of the pulmonary circulation in edema clearance in in vivo liquid-filled lungs between 4 and 8 hours of reperfusion. To study molecular modifications in ALC, we also measured expression levels of the epithelial sodium channel (ENaC) and sodium-potassium-adenosine triphosphatase (ATPase). We found that ALC was significantly lower in transplanted than in right native lungs ex vivo ($p<0.05$) and that transplanted lungs did not respond to the beta-adrenergic agonist terbutaline. Our in vivo study confirmed the ex vivo results. Molecular analyses revealed that ENaC messenger RNA but not sodium-potassium-ATPase was significantly decreased in transplanted lungs ($p<0.01$). Furthermore, there was a significant decrease in ENaC protein expression. Therefore, we conclude that the current investigation indicates that the lung injury caused by lung preservation and transplantation significantly reduces the edema clearance ability of transplanted lungs.
Descriptors: biochemistry and molecular biophysics, respiratory system, respiration, veterinary medicine, medical sciences, ischemia reperfusion injury, vascular disease, pulmonary edema, respiratory system disease, lung transplantation, clinical techniques, therapeutic and prophylactic techniques, molecular analyses, genetic techniques, laboratory techniques.

Takahashi, M., T. Nakamura, T. Toba, H. Kato, and Y. Shimizu (2003). **Cell transplantation of endothelial progenitor cells into lung improves pulmonary hypertension canine model.** *XXX Congress of the European Society for Artificial Organs (ESAO) on High Tech and Medicine, Aachen, Germany; September 03-06, 2003,*Vol. 26(7): 611,
Descriptors: cardiovascular system, transport and circulation, respiratory system, respiration, pulmonary hypertension, vascular disease, therapy, cell transplantation, clinical techniques, therapeutic and prophylactic techniques, neovascularization .

Vassalli, F., S. Pierre, V. Julien, Y. Bouckaert, S. Brimioulle, and R. Naeije (2001). **Inhibition of hypoxic pulmonary vasoconstriction by carbon monoxide in dogs.** *Critical Care Medicine.* 29(2): 359-66. ISSN: 0090-3493.
Abstract: OBJECTIVE: We tested the hypothesis that carbon monoxide might participate in the modulation of hypoxic pulmonary vasoconstriction (HPV) by prostacyclin (PGI2) and nitric oxide. DESIGN: Prospective, interventional study. SETTING: University laboratory. SUBJECTS: Nineteen intact anesthetized mongrel dogs. INTERVENTIONS: Right heart catheterization for the measurements of mean pulmonary artery pressure (Ppa), left atrial pressure estimated from occluded Ppa (Ppao), pulmonary capillary pressure (Pcp) calculated from the Ppa decay curve after balloon occlusion, and cardiac output (Q); inferior vena cava balloon for the control of Q by manipulation of venous return; ventilation in hyperoxia (fraction of inspired O2, 0.4) or in hypoxia (Fio2, 0.1); inhibition of cyclooxygenase by indomethacin (Indo); inhibition of nitric oxide synthase by NG-nitro-l-arginine (L-NA); inhibition of heme oxygenase by mesoporphyrin IX (SnMP); inhalation of nitric oxide (20 ppm); and inhalation of carbon monoxide (100 ppm). MEASUREMENTS AND MAIN RESULTS: The first seven dogs were weak responders to hypoxia as assessed by a hypoxia-induced increase in the gradient between Ppa and Ppao, measured at one level of Q kept

constant, by an average of only 2 mm Hg (p = NS). This HPV was markedly increased by the combined administration of Indo and L-NA. A further enhancement of HPV was observed after the addition of SnMP, leading to severe pulmonary hypertension with an average increase in Ppa to 39 mm Hg. Inhaled nitric oxide inhibited HPV only after the combined administration of Indo, L-NA, and SnMP. Inhaled carbon monoxide had no effect. The next 12 dogs were stronger responders to hypoxia, as assessed by a hypoxia-induced increase in the gradient between Ppa and Ppao, measured at several levels of Q, by an average of 3 mm Hg (p <.05). This HPV was of the same magnitude after administration of placebo (n = 6) or SnMP (n = 6). Addition of Indo enhanced HPV to the same extent in the placebo and in the SnMP groups. Addition of L-NA induced a further enhancement of HPV, which was, however, greater in the SnMP group. There was a slight increase in the capillary-venous segment relative to the arterial segment in hypoxic conditions, but the partitioning of pulmonary vascular resistance was otherwise unaffected by nitric oxide, carbon monoxide, or PGI2. CONCLUSIONS: Endogenous carbon monoxide modulates canine HPV only in the absence of nitric oxide. The vasodilation mediated by nitric oxide, PGI2, or carbon monoxide is essentially distributed between proximal and distal sites proportionally to the degree of constriction produced during hypoxia.
Descriptors: carbon monoxide, hypoxic pulmonary vasoconstriction (HPV), prostacyclin (PGI2), nitric oxide.

Wang, L., D.M. Zhu, X. Su, C.X. Bai, L.B. Ware, and M.A. Matthay (2004). **Acute cardiopulmonary effects of a dual-endothelin receptor antagonist on oleic acid-induced pulmonary arterial hypertension in dogs.** *Experimental Lung Research* 30(1): 31-42. ISSN: 0190-2148.
Abstract: The objective of this study was to evaluate the cardiopulmonary effects of a dual-endothelin (ET) receptor antagonist, Tezosentan, on oleic acid (OA)-induced acute lung injury with pulmonary arterial hypertension in dogs. Twelve Pentobarbital-anesthetized dogs with intravenous OA-induced acute lung injury (ALI) were divided into 2 groups. The control group (n=6) received saline treatment, whereas the treatment group (n=6) received the ET receptor antagonist, Tezosentan (1 mg/kg intravenous (IV)+1 mg/kg/h IV infusion). Cardiopulmonary parameters were monitored continuously for 1 hour. OA administration resulted in a significant increase in mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR) and a decrease in mean systemic arterial pressure (MSAP), systemic vascular resistance (SVR), and cardiac output (CO) in all-dogs. Tezosentan treatment markedly attenuated the pulmonary hypertension, with a 32% decrease in MPAP (from 23+-2 mm Hg to 15+-2 mm Hg; P<.01) and a 22% decrease in PVR (from 860+-105 dyncntdotscntdotcm-5 to 670+-96 dyncntdotscntdotcm-5; P<.01) at the end of study. MSAP and SVR were unchanged after Tezosentan treatment, and there was an increase in cardiac output and a decline in peak inspiratory pressure (PIP) in the Tezosentan group compared with the control group. These results indicate that the dual-ET receptor antagonist, Tezosentan, can attenuate the pulmonary hypertension induced by OA. Thus, dual-ET receptor antagonists such as Tezosentan may be useful in the management of acute pulmonary arterial hypertension, complicating the course of OA-induced lung injury.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, veterinary medicine, medical sciences, acute lung injury, injury, respiratory system disease, pulmonary arterial hypertension, respiratory system disease, vascular

disease, chemically induced, vascular disease, mean pulmonary arterial pressure [mpap], systemic vascular resistance.

Wang, M. and M.A. Lung (2003). **Adrenergic mechanisms in canine nasal venous systems.** *British Journal of Pharmacology* 138(1): 145-155. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: 1 We investigated the adrenergic mechanisms of the two venous systems that drain the nasal mucosa, thereby their exact role in eliciting nasal decongestion. The action of endogenously released noradrenaline and exogenous adrenergic agonists on different segments of the nasal venous systems, i.e. collecting (LCV, SCV) and outflow (SPV) veins of posterior venous system, collecting (ACV) and outflow (DNV) veins of anterior venous system and venous sinusoids of the septal mucosa (SM), were studied. In vitro isometric tension of the vascular segments was measured. 2 Transmural nerve stimulation (TNS) produced constriction in ACV, DNV and SM, primary constriction followed by secondary dilatation in LCV and SCV and dilatation in SPV. Tetrodotoxin (10-6 M) abolished all responses. Phentolamine (10-6 M), prazosin (10-6 M) and rauwolscine (10-7 M) inhibited the constriction in all venous vessels. Propranolol (10-6 M), atenolol (10-6 M) and ICI 118,551 (10-6 M) inhibited the relaxation in SPV but not in LCV and SCV. Phenylephrine and clonidine constricted whereas dobutamine and terbutaline relaxed all venous vessels dose-dependently. 3 These results indicate alpha1-, alpha2-, beta1- and beta2-adrenoceptors are present in both venous systems. TNS causes constriction of anterior venous system, venous sinusoids and posterior collecting veins primarily via postjunctional alpha2-adrenoceptors but relaxation of posterior outflow vein equally via postjunctional beta1- and beta2-adrenoceptors. The combined action of the two adrenergic mechanisms can reduce nasal airway resistance in vivo by decreasing vascular capacitance and enhancing venous drainage via the posterior venous system.
Descriptors: cardiovascular system, transport and circulation, pharmacology, respiratory system, respiration, nasal decongestion, respiratory system disease, transmural nerve stimulation, laboratory techniques, adrenergic mechanisms, isometric tension, nasal airway resistance, vascular capacitance, vasoconstriction, vasodilation, venous drainage.

Wang, P.M. and S. Kraman (2003). **A new fractal pattern of branching of the canine airway.** *FASEB Journal* 17(4-5): Abstract No. 875.7. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: respiratory system, lung, animal model, respiration, fractal pattern, irregular dichotomized fractal pattern, parent daughter pattern.

Wiedemann, K., E. Fleischer, and P. Dressler (2002). **Zur Geschichte der Seitentrennung der Atemwege.** *Anasthesiol Intensivmed Notfallmed Schmerzther.* 37(1): 8-15. ISSN: 0939-2661.
Abstract: Techniques to separate the airways to both lungs were employed in the laboratory by renowned physiologists like Pfluger and C. Bernard to study gas exchange. Pfluger's catheter, as used by Wolffberg in 1871 in the dog, essentially constituted an early example of endobronchial single lumen tube, and was to be the first airway separator introduced into man by Loewy and v. Schrotter in 1905 in experiments on circulation. As a variation of this device the carinal hook made ist appearance used by Hess in 1912 in rabbits. While the

endobronchial catheters afforded airtight access to only one lung at a time for concomitantly studying ventilation in both lungs, a short tracheal cannula was combined with one introduced into the left main bronchus by Head in 1889, constituting as it were the prototype of double lumen (DL) tubes applicable to rabbits and turtles even. Werigo described 1892 a coaxial DL-tracheostomy cannula for dogs which construction principle was adopted in the first DL-bronchoscope used in man. In lung surgery during the 30s and 40s the ventilated lung was prevented from drowning by pus or secretions from the lung under surgery by sealing off ist main bronchus, either by endobronchial intubation or by a bronchial blocker inserted alongside the endotracheal tube. This principle gave rise to sophisticated devices, from the fixed combination of tube and blocker to the present-day tube housing a movable blocker. Remarkably, DL-intubation in its proper sense then was performed in bronchospirometry only. This technique was introduced by Jacobaeus upon suggestion of Liljestrand when dissatisfied with the restriction to sequential spirometry by customary bronchoscopic catheterization, relying on Frenckner's ingenious DL-bronchoscope. Rubber DL-tubes were developed by Gebauer 1939 and Zavod 1940 exclusively with bronchospirometry in mind, even E. Carlens primarily constructed his tube to improve this procedure. After its usage in over 100 bronchospirometries it was introduced for the first time in November 1949 for its familiar purpose: the resection of a tuberculous abscess in the right upper lobe. Once introduced into thoracic anaesthesia, the DL-principle so far fostered a wide variety of tube designs.

Descriptors: bronchi, anatomy, histology, artificial respiration, history of techniques used, literature review, instrumentation, methods, anesthesiology.

Wilson, S.M., C.E. Mcallister, and J.R. Hume (2003). **Ip3 and ryanodine receptors and capacitative ca2+ entry in canine pulmonary arterial myocytes.** *Biophysical Journal* 84(2 Part 2): 391A. ISSN: 0006-3495.

NAL Call Number: 442.8 B5238

Descriptors: cardiovascular system, transport and circulation, metabolism, respiratory system, respiration

Yasukawa, T. (2002). **Effects of inversed ratio ventilation (irv) on intracranial pressure (icp) in dogs with pulmonary edema.** *Kawasaki Igakkai Shi* 28(4): 269-278. ISSN: 0386-5924.

Abstract: Although correlation between variations in the inspiratory to expiratory ratio (I:E ratio) and intracranial pressure (ICP) has not been clarified, the study of Mihira showed that IRV (at I:E ratios of 1.7:1, 2.3:1, and 4:1) does not influence ICP in dogs with normal or elevated ICP. In order to estimate the influence of lowered lung compliance on ICP during IRV, an additional study was designed to observe the effects of the I:E ratio=1:2 to 4:1 on ICP in 10 dogs with pulmonary edema induced by Oleic acid. Following baseline measurement of control ventilation (I:E ratio=1:2), lung edema was induced by venous injection of Oleic acid (0.05 mL/kg). After verifying the reduction of lung compliance, four different I:E ratios were applied in the order of I:E=1:2, 1.7:1, 2.3:1, and 4:1. Throughout the period of these measurements, PaCO2 constantly maintained normocapnia and arterial blood pressure was kept within normal range. Intracranial hemodynamics (ICP, cerebral perfusion pressure), lung mechanics (mean airway pressure (mAWP), peak inspiratory pressure (PIP), lung compliance), systemic hemodynamics (mean arterial pressure, mean pulmonary artery pressure,

central venous pressure, cardiac output), and blood gases were measured at 30 min under every I:E ratio ventilatory mode. In these dogs with pulmonary edema, mAWP significantly increased during IRV in comparison with that during control ventilation ($p<0.05$), but there was no significant difference in PIP between control ventilation and IRV. ICP remained unchanged during IRV (12.5+-4.2, 10.0+-2.9, 11.1+-2.2, 11.3+-2.7 at I:E=1:2, 1.7:1, 2.3:1 and 4:1, respectively). This study suggested that IRV (at I:E ratios of 1.7:1, 2.3:1, and 4:1), which can minimize ventilator-induced lung injury, has no influence on ICP. Therefore, IRV may be one beneficial option as ventilation strategy for acute respiratory distress syndrome with intracranial hypertension.

Descriptors: methods and techniques, nervous system, neural coordination, respiratory system, respiration, acute respiratory distress syndrome, respiratory system disease, intracranial hypertension, nervous system disease, vascular disease, pulmonary edema, inversed ratio ventilation, laboratory techniques, intracranial pressure, mean airway pressure.

Language of Text: Japanese.

Sensory Organs

Barros, P.S.M., C.F. Padovani, V.V. Silva, and S.B.M. Barros (2001). **Oxidative stress after lens phaco-emulsification in dogs**. *IOVS* 42(4): S13.
Descriptors: methods and techniques, sense organs, sensory reception, anterior chamber paracentesis, diagnostic method, applanation tonometry, indirect ophthalmoscopy, lens phaco emulsification, surgical method, therapeutic method, slit lamp biomicroscopy, oxidative stress, meeting abstract.

Bock, P., A. Beineke, S. Techangamsuwan, W. Baumgartner, and K. Wewetzer (2007). **Differential expression of HNK-1 and p75(NTR) in adult canine Schwann cells and olfactory ensheathing cells in situ but not in vitro.** *Journal of Comparative Neurology* 505(5): 572-85.
NAL Call Number: QP351.J68
Abstract: Olfactory ensheathing cells (OECs) are promising candidates for autologous cell transplantation therapies of nervous system injury and disease. Large animal models are relevant for transferring experimental data into clinical practice. In vivo studies have suggested that adult canine OECs may display similar regenerating capacities as their rodent counterpart. However, data on their molecular phenotype required for generating pure cell preparations are still scarce. In the present study, we comparatively analyzed expression of the carbohydrate HNK-1 epitope and the neurotrophin receptor p75(NTR) in adult canine Schwann cells and olfactory ensheathing cells in situ and in vitro. Myelinating and nonmyelinating Schwann cells in situ exclusively expressed HNK-1 and p75(NTR), respectively, whereas OECs were negative for both markers. In vitro, OECs and Schwann cells shared cell surface expression of p75(NTR) but not of HNK-1, which could be detected transiently in intracellular vesicles. This suggests that Schwann cells and OECs in vitro phagozytose HNK-1+ cellular debris. The cultivation-induced downregulation of HNK-1 expression in Schwann cells and upregulation of p75(NTR) in OECs argues for the possibility that axonal signals control the expression of both markers in situ. Whereas HNK-1 expression in Schwann cells is most likely controlled by signals inducing myelination, e.g., neuregulin, the mechanisms that may suppress p75(NTR) expression in OECs in situ remain to be elucidated. Interestingly, HNK-1 expression in the adult dog was found in both sensory and motor nerve myelinating Schwann cells. This is reminiscent of humans and differs from rodents; it also underscores the importance of large animal models for translational research. (c) 2007 Wiley-Liss, Inc.
Descriptors: antigens, cd57 metabolism, biological markers metabolism, dogs, olfactory pathways metabolism, receptor, nerve growth factor metabolism, schwann cells metabolism, age factors, cells, cultured, fluorescent antibody technique, maxillary nerve cytology, models, animal, olfactory bulb cytology, olfactory mucosa cytology, olfactory pathways cytology, schwann cells cytology, sciatic nerve cytology, species specificity, stellate ganglion cytology, sympathetic nervous system cytology, trigeminal nerve cytology.

Bonatti, J.A., S.J. Bechara, M.W. Dall'Col, F.B. Cresta, P.C. Carricondo, and N. Kara Jose (2007). **A fibrin-related line of research and theoretical possibilities for the use of fibrin glue as a temporary basal membrane in non-perforated corneal ulcers and in photorefractive keratectomy (PRK)-operated corneas.** *Arquivos Brasileiros De Oftalmologia* 70(5): 884-9. ISSN: 0004-2749.

Abstract: PURPOSE: To report a specific line of research developed at the University of Sao Paulo/Brazil on fibrin glue used for sealing corneal perforations and the perspectives of use on non-perforated corneal ulcers and photorefractive keratectomy-operated corneas. METHODS: To describe fibrin glue manufacture, development of a device to test the glued perforated corneal area resistance, subsequent experimental investigations of the use of the fibrin glue in corneal perforations, reporting its efficacy, mechanical resistance experiments and histological study. Finally, the medical literature basis is searched to propose studies on the use of fibrin as a temporary basal membrane on non-perforated corneal surfaces like non-infectious corneal ulcers and on post-photorefractive keratectomy corneal surfaces. RESULTS: The development of fibrin glue, the device for resistance experiments, the efficacy, resistance and histological studies on fibrin glue used for sealing corneal perforations are reported as well as the scientific literature basis for the proposed studies on the use of fibrin as a temporary basal membrane on non-perforated corneas like non-perforated corneal ulcers and photorefractive keratectomy corneal surfaces. CONCLUSION: A specific line of research was reported on fibrin glue to seal corneal perforations at the University of Sao Paulo/Brazil and the theoretical perspectives for the use of fibrin in non-perforated corneal ulcers and on photorefractive keratectomy-operated corneas in an attempt to reduce corneal haze.

Descriptors: corneal diseases drug therapy, corneal ulcer drug therapy, fibrin tissue adhesive therapeutic use, membranes, artificial, research design, tissue adhesives therapeutic use, cornea injuries, corneal diseases surgery, dogs, intraocular pressure drug effects, lasers, excimer, models, animal, photorefractive keratectomy.

Colitz, C., A. Whittington, and J. Warren (2002). **Measurement of p16 in canine lens epithelial cells in response to oxidative stress.** *Annual Meeting of the Association For Research in Vision and Ophthalmology, Fort Lauderdale, Florida, USA; May 05-10, 2002,*

Abstract: Purpose: We previously demonstrated that lens epithelial cells (LEC) have telomerase activity. Neoplastic cells can have a reciprocal relationship between telomerase activity and levels of p16. Telomere length, development of senescence and p16 expression are influenced by oxidative stress. Since oxidative stress is implicated in cataractogenesis, the purpose of these experiments was to determine how exposure of LEC to tertiary butyl-hydroperoxide (TBHP) induced oxidative stress affects telomerase activity and p16 expression. Methods: Fresh canine lenses were incubated in keratinocyte growth medium and M199 with serum. In the first experiment, lenses were exposed to media with or without 0.5mM TBHP for varying time periods (8 lenses per group; 15, 25, 40, 60, 150 minute and overnight) In the second experiment, lenses were exposed to media containing 0.5 mM TBHP for one hour and then recovered in media without TBHP for varying time periods (8 lenses per group; 5, 60, 180 minute and overnight recoveries, no recovery, control group without treatment). Following these treatments, the anterior lens capsules with adhered LEC were collected. P16

levels in LEC were measured by ELISA using a dig- labeled antibody to p16. Telomerase activity was measured by TRAP-ELISA. Results: There was no change in p16 levels following direct exposure to TBHP. Telomerase activity was significantly up-regulated at the 150 minute point ($p<0.01$). The second group had significantly lower p16 levels (0.179-0.280) than the control group (0.441, $p<0.05$) at 15, 25, 40, 60, 180 minute and overnight recovery. Telomerase activity was significantly elevated at the 15, 60 and 180 minute and overnight recovery times (2.173-2.268) vs control (1.547, $p<0.02$). Conclusion: p16 is a cell cycle inhibitor that is down-regulated when telomerase activity is up-regulated in many tumors contributing to unregulated growth. Acute exposures with TBHP did not alter p16 or telomerase activity (except at 150 minutes) which may indicate that either the length of exposure may too short to cause changes in the proteins or the proteins' half-lives may be too long for changes to be seen in this experiment. In the recovery experiment, telomerase activity was up-regulated and p16 was down-regulated, similar to tumor cells. The recovery process following oxidative stress in LEC may involve proliferation of cells to replace damaged or dead cells. Future experiments will further examine the proliferative capacity of LEC under similar conditions and the response of p16 when LEC are chronically exposed to oxidative stress.

Descriptors: biochemistry and molecular biophysics, sense organs, sensory reception, tumor biology, tumor, neoplastic disease, elisa, immunologic techniques, laboratory techniques, trap elisa, oxidative stress.

Coppens, A.G., I. Salmon, C.W. Heizmann, R. Kiss, and L. Poncelet (2003). **Postnatal maturation of the dog stria vascularis: an immunohistochemical study.** *Anatomical Record* 270A(1): 82-92. ISSN: 0003-276X.

NAL Call Number: QL801 .A53

Abstract: The lateral wall of the dog cochlear duct was investigated by classical staining and immunohistochemistry for NaK/ATPase beta2 isoform, cytokeratins (Cks), vimentin, nestin, and S100A6 during the postnatal cochlear maturation, i.e., from birth to postnatal day 110. The dog stria vascularis was immature at birth. Fine melanin granules were evident in the stria from the second week of life, and melanin concentration increased drastically beyond the first month. The marginal cells were NaK/ATPase- and Ck-positive; intermediate cells were either nestin- and S100A6-positive or vimentin-positive; the basal cells were vimentin-positive; the capillary endothelium showed vimentin and nestin labeling; the cell layer underlying the stria was nestin-positive. The fibrocytes of the spiral ligament and spiral prominence expressed nestin and vimentin. The epithelial cells overlaying the spiral prominence and the external sulcus were Ck-positive, and transiently nestin- and vimentin-positive. Double immunolabeling, for S100A6 and either nestin, vimentin, or NaK/ATPase, and for nestin and vimentin suggested the presence of two distinct intermediate cell types. The results enabled us to differentiate the cell types forming the lateral wall of the dog cochlear duct, and to follow their postnatal maturation. This study may form a basis for future investigations about spontaneous cochleosaccular degeneration in dogs. This species is an important companion animal, and a possible model for the study of comparable diseases in humans.

Descriptors: biochemistry and molecular biophysics, development, sense organs, sensory

reception, spontaneous cochleosaccular degeneration, ear disease, pathology, double immunolabeling, immunologic techniques, laboratory techniques, immunohistochemistry.

Ford, M.M., R. Bragadottir, E. Rakoczy, and K. Narfstrom (2003). **Long - term visual behavior correlates with functional electroretinographic assessment after gene transfer in rpe65 - / - dogs**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*

Abstract: Purpose: To assess the long-term effects of subretinal rAAV.RPE65 gene transfer on functional vision in RPE65-/- dogs. Methods: Five dogs homozygous for the RPE65 null mutation and 2 unaffected, visually normal control dogs were included. Affected animals had been treated subretinally with 70 - 100 mul of rAAV.RPE65 gene construct (2 X 1012 particles/ml) in the right eye (OD), and 0 - 100 mul of rAAV.GFP (2 X 1010 transforming units/ml) in the left eye (OS). Treatment for control dogs was 75 - 100 mul of the latter OD and 100 mul of BSS OS. Evaluations from pre-surgical and follow-up bilateral full-field electroretinograms (ERGs) 6 mo post-surgery were obtained. Objective assessment of functional vision was performed 3 and 6 mo post-operatively by counting the number of collisions made by the dogs as they negotiated a maze of obstacles in dim and day light conditions. Vision in individual eyes was also assessed 6 mo post-surgery. Results: Three mo after gene therapy there was a higher number of collisions in dim light than in day light ($p<0.008$) among affected dogs; a difference not evident 6 mo post-operatively. In day light conditions, no difference was noted between control and affected animals at 3 or 6 mo. In dim light, affected dogs had a higher number of collisions than control dogs at 3 ($p<0.004$) but not 6 mo post-operatively. Fewer collisions ($p<0.1$) were noted in day and dim light when only OD was exposed compared with exposure of only OS in the affected dogs. Post-surgery, high intensity scotopic stimuli and 30 Hz flicker ERG amplitudes were elevated ($p<0.04$) over pre-operative recordings in OD, and elevated over post-operative recordings in OS as well ($p<0.032$). Further, post-operative single flash photopic b-wave amplitudes for OS were increased over pre-operative values ($p<0.05$). Conclusions: Progressive improvement in functional binocular and monocular (OD) vision up to 6 mo after gene transfer was found by objective behavioral testing. The long-term visual improvement correlated with a significant increase in post-operative ERG amplitudes, mainly in OD but also with measurable effects in OS.

Descriptors: methods and techniques, molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, functional electroretinography, laboratory techniques, gene transfer, genetic techniques, visual behavior.

Glover, T.L., M.P. Naisse, and M.G. Davidson (1995). **Effects of topically applied mitomycin-C on intraocular pressure, facility of outflow, and fibrosis after glaucoma filtration surgery in clinically normal dogs.** *American Journal of Veterinary Research* 56(7): 936-940. ISSN: 0002-9645.

NAL Call Number: 41.8 Am3A

Abstract: The effects of mitomycin-C on intraocular pressure (IOP), facility of outflow (C), and Tenon's capsule fibrosis were studied over 60 days in 10 clinically normal dogs. A 1-piece, silicone glaucoma implant was surgically implanted into both eyes; the filtration

site of one eye was treated with a single, 5-minute intraoperative application of mitomycin (0.5 mg/ml), and the fellow eye was treated in a similar manner with balanced salt solution. There were no significant differences in preoperative IOP or C-values between treatment groups. Mean IOP in eyes of both groups initially decreased from the preoperative value, but returned to the baseline value by day 21. Mean facility of aqueous outflow (C-value) increased in all eyes during the first 14 days (mitomycin-C-value = 2.26 +/- 0.72; control C-value = 2.38 +/- 0.81), then reached a plateau that was significantly higher than the baseline value in mitomycin (P = 0.039) and control (P = 0.041) eyes. Histologic evaluation revealed all implants surrounded by a connective tissue capsule composed of regular dense collagen and fibroblasts that was significantly (P = 0.003) thinner in the mitomycin-treated (scleral side = 167 +/- 62 micrometer; conjunctival side = 122 +/- 41 micrometer) than the control (scleral side = 261 +/- 92 micrometer; conjunctival side = 180 +/- 48 micrometer) group. There were, however, no significant differences in IOP or C-values between groups at any postoperative time interval. Results of this study indicate that intraoperative treatment with mitomycin suppresses, but does not prevent fibrosis around silicone filtering implants.
Descriptors: glaucoma, surgery, mitomycin, topical application, internal pressure, fibroblasts, body fluids, flow, drug effects, aqueous humor outflow.
Notes: Includes references.

Hunter, L.S., D.J. Sidjanin, G.M. Acland, M. Villagrasa, and G.D. Aguirre (2003). **Evaluation of pax6 for mutations causing inherited ocular diseases in canine models**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*
Abstract: Purpose: Normal ocular development is dependent on the transcription factor PAX6. Mutations in PAX6 can result in aniridia, cataract, glaucoma, foveal hypoplasia and optic nerve hypoplasia in man. In mice, mutations in Pax6 cause the Small Eyepheonotype characterized by microphthalmia, abnormal lens and iris development and cataract. The purpose of this study is to evaluate the canine PAX6 gene for mutations causal to inherited ocular disease in canine models. Methods: Nine breeds of dog were identified having inherited forms of ocular disease for which PAX6 is a candidate gene. Two affected dogs from each breed were evaluated and their PAX6 sequence compared to canine wildtype sequence. Genomic DNA was prepared from whole blood and exons were scanned using intronic primers. Since the sequence for intron 4 could not be amplified, exon 4 was sequenced using primers in intron 3 and at the 3' end of exon 4, and exon 5 was sequenced using primers at the 5' end of exon 5 and in intron 5. Similarly, because of a homopolymer in the 3'UTR, exon 13 was evaluated using primers in intron 12 and at the 3' end of exon 13. Results: Thirteen exons plus an alternatively spliced exon (5a) are being examined in nine dog breeds with inherited eye diseases including cataracts, microphthalmia, persistent pupillary membranes, rod-cone dysplasia 2, cone-rod dystrophy 1 and 2, and aniridia. To date, no mutations associated with disease have been identified in the exons so far examined including the non-coding exons 1, 2, and 3. In addition to a previously identified SNP in intron 8, a single nucleotide change was identified in exon 7. This was a Cytosine -> Thymine change which did not result in an amino acid change. Microsatellites have been identified in exons 1 and 2, and in introns 6 and 7 which may facilitate linkage analysis. Conclusions: PAX6 plays an integral role in ocular development and mutations in this transcription factor cause different disease

phenotypes. Evaluating canine models may identify novel disease phenotypes associated with PAX6 mutations.

Descriptors: molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, aniridia, congenital disease, eye disease, genetics, cataract, cone rod dystrophy 1, cone rod dystrophy 2, inherited ocular disease, genetic disease, genetics, microphthalmia, persistent pupillary membrane, linkage analysis, genetic techniques, laboratory techniques, disease phenotype, ocular development.

Kador, P.F., K. Blessing, and M. Wyman (2003). **The results of combretastatin in galactose - fed dogs with diabetes - like proliferative retinopathy**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*

Abstract: Purpose: Combretastatin A-4 (CA4P) is a vascular targeting agent that has been reported to be capable of destroying newly formed capillary endothelial cells in growing vessels. The net effect of this drug has been to rapidly shut off blood flow in newly growing vessels and, as a result, regress neovascularization. The purpose of this study was to determine whether retinal neovascularization which results in altered retinal vessel blood flow and retinal permeability in the long-term galactose-fed dog can be halted with CA4P. Methods: All experiments conform to the ARVO Resolution on the Use of Animals in Research and NIH ACUC Guidelines. Eight beagles fed 30% galactose diet for 80-104 months and four age-matched control dogs were surgically made aphakic. Following recovery the dogs were divided into two groups each containing 4 galactose-fed dogs and 2 age-matched controls dogs with each group receiving CA4P either as sub-Tenon's injections administered at the corneoscleral junction or intravitreal injections. Six weeks after initial CA4P treatment all dogs also received systemic (IV) injections of CA4P. The extent of neovascularization and affect of CA4P administration were monitored by fluorescein angiography and color and monochromatic fundus photography at 2-week intervals. Results: Although CA4P was well tolerated by the healthy eyes of the control animals its administration to galactose-fed dogs was associated with corneal edema and increases in IOP after sub-Tenon's and intraocular injections. All galactose-fed dogs demonstrated retinal neovascular lesions and these were not ameliorated by either sub-Tenon's, intravitreal or systemic CA4P administration. Conclusions: Neovascularization in this animal model progresses over a period of years similar to that observed clinically. The failure of CA4P to ameliorate neovascularization suggests that chronic, long-term administration is required to destroy the slowly growing retinal endothelial cells.

Descriptors: cardiovascular system, transport and circulation, metabolism, pharmacology, sense organs, sensory reception, aphakia, eye disease, diabetes like proliferative retinopathy, endocrine disease, pancreas, metabolic disease, retinal blood vessel blood flow, retinal neovascularization.

Komaromy, A.M., J.J. Alexander, A.E. Cooper, V.A. Chiodo, L.G. Glushakova, G.M. Acland, W.W. Hauswirth, and G.D. Aguirre (2008). **Targeting gene expression to cones with human cone opsin promoters in recombinant AAV.** *Gene Therapy* 15(14): 1049-55.

Abstract: Specific cone-directed therapy is of high priority in the treatment of human hereditary retinal diseases. However, not much information exists about the specific targeting of photoreceptor subclasses. Three versions of the human red cone opsin promoter (PR0.5,

3LCR-PR0.5 and PR2.1), and the human blue cone opsin promoter HB569, were evaluated for their specificity and robustness in targeting green fluorescent protein (GFP) gene expression to subclasses of cones in the canine retina when used in recombinant adeno-associated viral vectors of serotype 5. The vectors were administered by subretinal injection. The promoter PR2.1 led to most effective and specific expression of GFP in the long- and medium-wavelength-absorbing cones (L/M cones) of normal and diseased retinas. The PR0.5 promoter was not effective. Adding three copies of the 35-bp LCR in front of PR0.5 lead to weak GFP expression in L/M cones. The HB569 promoter was not specific, and GFP was expressed in a few L/M cones, some rods and the retinal pigment epithelium. These results suggest that L/M cones, the predominant class of cone photoreceptors in the retinas of dogs and most mammalian species can be successfully targeted using the human red cone opsin promoter.

Descriptors: gene therapy methods, promoter regions, genetic, retinal cone photoreceptor cells metabolism, rod opsins genetics, targeted gene repair, color vision defects metabolism, color vision defects therapy, dependovirus genetics, dogs, gene expression, genetic vectors administration and dosage, green fluorescent proteins genetics, injections, models, animal, transduction, genetic methods, transgenes.

Notes: Comments: Erratum In: Gene Ther. 2008 Jul;15(14):1073^^Glushakova, L G [added].

Old, S.E., D.A. Carper, and T.C. Hohman (1995). **Na,k-atpase response to osmotic stress in primary dog lens epithelial cells**. *Investigative Ophthalmology and Visual Science* 36(1): 88-94. ISSN: 0146-0404.

Abstract: Purpose: Na,K-ATPase activity increases in lens cells exposed to hypertonic stress. To test whether the increase in activity involves stimulation of Na,K-ATPase expression, dog lens epithelial cells were subjected to hypertonic stress, and the time course of Na,K-ATPase protein and mRNA response was measured. Methods: Primary cultures of dog lens epithelial cells were maintained in isotonic or hypertonic media over the course of several days. Rubidium-86 uptake measurements, immunoreactive protein, and northern blot analysis were performed. Results: Dog lens epithelial cells exposed to hypertonic stress from culture medium supplemented with 150 mM NaCl or 250 mM cellobiose showed a twofold increase in Na,K-ATPase activity. The increase in activity was blocked by cycloheximide and was reversible when the cells were returned to isotonic medium. This activity was unaffected by the aldose reductase inhibitor, tolrestat. Na,K-ATPase protein and mRNA levels increased in cells exposed to medium containing 150 mM NaCl. Northern blot analysis showed that the alpha-1 and beta-1 mRNA levels increased as early as 6 hours and maximally increased 1.5-fold to twofold by 12 to 24 hours. Conclusions: Elevation of Na,K-ATPase activity in dog lens epithelial cells exposed to hypertonic stress was associated with increased expression of Na,K-ATPase subunit mRNAs and was dependent on protein synthesis. These results suggest that upregulation of the enzyme activity is the result of an induction of Na,K-ATPase.

Descriptors: biochemistry and molecular biophysics, cell biology, enzymology, biochemistry and molecular biophysics, metabolism, sense organs, sensory reception, enzyme activity up regulation, hypertonic stress, protein synthesis, sodium potassium atpase.

Panzan, C.Q., D. Guven, J.D. Weiland, R.R. Lakhanpal, M. Javaheri, E.J. de Juan, and M.S. Humayun (2004). **Retinal thickness in normal and RCD1 dogs using optical coherence tomography.** *Ophthalmic Surgery, Lasers and Imaging* 35(6): 485-93. ISSN: 1542-8877.

Abstract: BACKGROUND AND OBJECTIVE: To compare retinal thickness and retinal nerve fiber layer (RNFL) thickness values obtained by optical coherence tomography (OCT) in normal dogs and dogs with rod-cone dysplasia type 1 (RCD1). MATERIALS AND METHODS: Eight eyes of 6 normal hound-bred dogs and 12 eyes of 6 dogs with RCD1, 2 to 5 years of age, were examined using the Fast RNFL Thickness, Fast Macular Thickness, and line scan protocols of OCT. RESULTS: Retinal thickness was significantly higher in the tapetal fundus than in the non-tapetal fundus, in both normal (P = .0036) and RCD1 (P < .0001) dogs. Superotemporal, superonasal, and inferior retinal thickness values were significantly higher in normal dogs (P < .0001). Area centralis thickness was 183.5 +/- 10.66 microm in normal dogs and 136.16 +/- 13.12 microm in RCD1 dogs (P < .0001). There was no difference in RNFL thickness between normal and RCD1 dogs (P > .05). CONCLUSION: OCT scanning in dogs is considered to be a useful method of evaluation in future retinal studies in this animal model.

Descriptors: hound -bred dogs, rod-cone dysplasia type 1 (RCD1), optical coherence tomography (OCT), retinal thickness, tapetal fundus, retinal nerve fiber layer.

Pearce Kelling, S.E., A. Nickle, P. Didia, J. Jordan, G. Antonini, G. Aguirre, and G. Acland (2003). **Retinal disease phenotype of the rdsf briard - derived rpe65 - / - dog**. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, USA; May 04-08, 2003,*

Abstract: Purpose. A naturally occurring canine RPE65-/- mutation, the cause of canine Lebers congenital amaurosis in the briard dog, provides a large animal model for the human disease. A laboratory strain of dogs has been derived from an affected male briard bred to colony dogs at the Retinal Disease Study Facility (RDSF), and used for asssesment of potential therapies. To establish baseline data, we have characterized the morphologic disease of the RDSF-derived strain of dogs. Methods. Age matched RPE65-/- and wt dogs were enucleated at different ages and their eyes were either fixed in paraformaldehyde, embedded in OCT, and then frozen-sectioned for immunocytochemical examination, or fixed in glutaraldehyde/formaldehyde, epon embedded and sectioned for morphological evaluation. Results. Examination of epon sections showed that by 16 weeks the rod outer segments (ROS) are slightly irregular in the RPE65-/- mutant. By 11 months the inferior retina showed very early retinal degeneration, characterized by shortening of ROS, but there was no apparent loss of outer nuclear layer nuclei. In contrast, disease in the superior retina was limited to ROS irregularities similar to that observed at 4 months. No morphological abnormalities were apparent in OCT embedded frozen sections except for lipid inclusions. These were present in the RPE of all diseased animals and were larger and more numerous in older animals. RPE65 protein was absent in the mutant dogs; all other retinal antigens examined (e.g. cone opsin, rhodopsin and insoluble IPM cone sheath) were expressed similarly between the mutant and wild type eyes. Conclusions. The RPE65-/- mutant shows abnormalities limited to the ROS at a young age; these progress slowly to a mild degeneration that is first observed in the inferior retina in the older animal. The preservation of photoreceptors during the first year of life gives a broad time window to examine the efficacy of therapies in this class of retinal diseases.

Descriptors: molecular genetics, biochemistry and molecular biophysics, sense organs, sensory reception, Lebers congenital amaurosis, congenital disease, eye disease, genetic disease, retinal degeneration, retinal disease, optimal computed tomography, clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques, immunocytochemical examination, immunologic techniques, retinal disease study facility, disease phenotype.

Rasmussen, C.A., B.T. Gabelt, and P.L. Kaufman (2002). **Effect of win 55,212-2 on monkey and dog ciliary muscle in vitro.** *Annual Meeting of the Association For Research in Vision and Ophthalmology, Fort Lauderdale, Florida, USA; May 05-10, 2002,*

Abstract: Purpose: To investigate the effect of WIN 55,212-2, a cannabinoid that has been reported to lower intraocular pressure (IOP) in primates, and its diluents on monkey and dog isolated ciliary muscle (CM) Methods: CM strips were mounted in a perfusion apparatus and contractile force measured in both the longitudinal (LONG) and circular (CIRC) vectors. CM was perfused with Krebs solution at a rate of 8 or 10 ml/min. Effects of WIN (10muM-40muM) were measured on carbachol (CARB; 1muM) precontracted CM and on CM at resting tension. Effects of different flow rates, DMSO and 2-hydroxypropyl-beta-cylodextrin (HPbCD) concentrations on the CM response were also measured. Results: Monkey CM response (mean+-s.e.m.) to CARB was 190+-72.1 mg LONG and 112+-37.8 mg CIRC (n=6). DMSO decreased the CARB response dose dependently by up to 57+-31.8% LONG and 45+-11.9% CIRC with 4% DMSO (n=6). The addition of 10 - 40muM WIN to CARB/4% DMSO resulted in minimal changes of up to -9+-13% LONG and -9+-19% CIRC (n=3) respectively, relative to the CARB/4%DMSO response. CM resting tension in Krebs/4% DMSO was 49.2+-25.0 mg LONG and 71.7+-16.1mg CIRC (n=3). The addition of 10 - 40muMWIN/4% DMSO resulted in changes of up to -30+-22% LONG, and -8+-4% CIRC respectively. None of the WIN responses seemed to be dose related. DMSO or HPbCD alone reduced resting tension by 32+-32% LONG and 6+-3% CIRC (n=10). CM response to CARB/2.25 or 4.5% HPbetaCD was increased by 7% LONG and 12% CIRC compared to CARB alone. WIN responses with HPbetaCD were similar to those obtained with DMSO. Dog CM contraction to CARB was much stronger than monkey (269+-129.3mg LONG and 178+-60.5mg CIRC, n=6). Otherwise the responses to WIN were similar. The optimal fluid flow rates through the chamber were 8 -10ml/min based on responses to CARB. Conclusion: WIN has minimal but variable effects on resting CM tension and CARB stimulated CM contraction. DMSO, and to a lesser extent, HPbetaCD can alter CARB contraction and resting tension; therefore care must be exercised in interpreting the responses to compounds which must be dissolved in these vehicles. Dog CM contracts strongly to CARB but its use as an alternative to monkey CM must be further evaluated with other compounds.

Descriptors: biochemistry and molecular biophysics, muscular system, movement and support, sense organs, sensory reception, intraocular pressure.

Tameesh, M.K., R.R. Lakhanpal, G.Y. Fujii, M. Javaheri, T.H. Shelley, S. D'anna, A.C. Barnes, E. Margalit, M. Farah, E.J. De Juan, and M.S. Humayun (2004). **Retinal vein cannulation with prolonged infusion of tissue plasminogen activator (t-pa) for the treatment of experimental retinal vein occlusion in dogs**. *American Journal of Ophthalmology* 138(5):

829-839. ISSN: 0002-9394.
Descriptors: animal model, enucleated porcine eyes, in vivo canine eyes, experimental branch retinal vein occlusion, local thrombolytic agents, safety testing.,retinal vein cannulation, surgical technique, microcatheter injection, tissue plasminogen activator (t-PA).

Toxicology

Cai, Y., Q. Ma, L. Zhang, J. Zhao, M. Zhu, W. Hu, P. Jiang, and W. Yuan (2004). **[Therapeutic effects of rhEPO, rhG-CSF on sulfur mustard induced toxicity in dogs]**. *Wei Sheng Yan Jiu; Journal of Hygiene Research* 33(6): 649-51. ISSN: 1000-8020.

Abstract: OBJECTIVE: To evaluate the therapeutic effects of recombinant human erythropoietin (rhEPO) and recombinant human granulocyte colony stimulating factor (rhG-CSF) on sulfur mustard (SM) induced toxicity in dogs. METHODS: Ten dogs were used as the animal model. Control group had four dogs while treatment group had six. Half an hour after subcutaneously injected with 12 mg/kg (body weight) of SM, the dogs of the treatment group were treated by rhEPO, rhG-CSF and other medicines. General examinations of blood were measured before injecting SM and were continually watched for a week after poisoning. RESULTS: Three dogs in control group died in three days after poisoning, dogs in treatment group all survived. WBC of the control group decreased significantly 3 days after poisoning. RBC of the control group had a slight increase at first, then came down. While WBC and RBC of treatment group remained constant. LYM of both groups descended notably right after poisoning, especially in control group. Two days after poisoning, RC in treatment group began to rise and remained at high level for about a week. No obvious changes of RC in control group were found. CONCLUSION: The use of rhEPO and rhG-CSF after SM exposure can stimulate the growth of the erythrocyte, reticulocyte and leucocyte in dogs. Therefore, rhEPO and rhG-CSF may be significant assistant drugs in future experiment of SM.

Descriptors: toxicity, induced, sulfur mustard, poisoning, recombinant human erythropoietin (rhEPO), recombinant human granulocyte colony stimulating factor (rhG-CSF), blood examination, therapeutic effects .

Language of Text: Chinese; Non-.

Notes: Library: National-Library-of-Medicine.

Carballo Jane, E., L.S. Gerckens, S. Luell, A.S. Parlapiano, M. Wolff, S.L. Colletti, J.R. Tata, A.K. Taggart, M.G. Waters, J.G. Richman, M.E. McCann, and M.J. Forrest (2007). **Comparison of rat and dog models of vasodilatation and lipolysis for the calculation of a therapeutic index for GPR109A agonists.** *Journal of Pharmacological and Toxicological Methods* 56(3): 308-16. ISSN: 1056-8719.

NAL Call Number: QP901.J6

Abstract: INTRODUCTION: GPR109A is the receptor mediating both the antilipolytic and vasodilatory effects of nicotinic acid. In order to develop agonists for GPR109A with improved therapeutic indices we have sought to optimize animal models that evaluate both nicotinic acid-mediated inhibition of lipolysis and stimulation of vasodilatation. The rat and the dog have previously been used to study the antilipolytic effects of nicotinic acid, but no optimal vasodilatation model exits in either species. METHODS: We have developed a vasodilatation model in the rat that measures changes in ear perfusion using laser Doppler flowmetry. In the dog, we have developed a model of vasodilatation measuring changes in red

color values in the ear, using a spectrocolorimeter. Effects of GPR109A agonists on lipolysis were measured in both species after oral dosing of compounds, and measuring plasma levels of free fatty acids. RESULTS: In both rat and dog, GPR109A agonists induce dose- and time-dependent vasodilatation, similar to that observed in humans. Vasodilatation is inhibited in both species with cyclooxygenase inhibitors or a specific DP1 receptor antagonist, indicating that, as in man, nicotinic acid-induced vasodilatation in rats and dogs is mainly mediated by the release of PGD(2). DISCUSSION: Our results show that both rat and dog are useful models for the characterization of GPR109A agonists. A therapeutic index for GPR109A agonists can be calculated in either species.

Descriptors: lipolysis drug effects, nicotinic agonists pharmacology, receptors, g protein coupled agonists, vasodilation drug effects, anti inflammatory agents, non steroidal administration and dosage, anti inflammatory agents, non steroidal pharmacology, antilipemic agents administration and dosage, antilipemic agents pharmacology, dogs, dose response relationship, drug, drug evaluation, preclinical methods, drug monitoring methods, fatty acids, nonesterified blood, indomethacin administration and dosage, indomethacin pharmacology, inhibitory concentration 50, injections, subcutaneous, models, animal, niacin administration and dosage, niacin pharmacology, nicotinic agonists administration and dosage, pyrazines administration and dosage, pyrazines pharmacology, rats, rats, sprague dawley, receptors, nicotinic metabolism.

Fekri, A., N. Semir, S. El Atrous, L. Besbes, B. Riadh, B. Mohamed, M. Soudani, J. Eurin, C. Barthelemy, M. El Ayeb, D. Koussay, and A. Carayon (2003). **A canine study of immunotherapy in scorpion envenomation**. *Intensive Care Medicine.* 29(12): 2266-2276. ISSN: 0342-4642.

Abstract: Objective: To evaluate the effects of scorpion venom and antivenom in experimental envenomation. Design: Prospective, controlled animal study. Setting: University research laboratory Subjects: Twenty-nine anesthetized and ventilated dogs. Interventions: The first group of animals had venom alone (0.05 mg/kg). Animals from the second group had simultaneous administration of 10 ml of scorpion antivenom (SAV). In the third and fourth groups, 10 ml and 40 ml SAV, respectively, were injected 10 min following venom. Measurements and results: Hemodynamic parameters using right heart catheter were recorded and dosage of catecholamines, neuropeptide Y (NPY), endothelin-1, and atrial natriuretic peptide (ANP) were performed at baseline and during 60 min following envenomation. In the control group, at 5 min, there was a sharp increase in pulmonary artery occluded pressure (PAOP, from 2 mmHg to 23 mmHg), mean arterial pressure (MAP, from 125 mmHg to 212 mmHg) and systemic vascular resistance (SVR, from 2,450 dyn sec-1 m5 to 5,775 dyn sec-1 m5, P<0.05 for all). Heart rate, cardiac output, and stroke volume decreased. There was a 40-fold increase in epinephrine and norepinephrine plasma concentrations. Circulating NPY and ANP dosages increased too. PAOP and MAP decreased thereafter to reach baseline levels. Simultaneous administration of SAV with venom totally offset the hallmarks of scorpion envenomation. Delayed administration of SAV at any dosage failed to alter the features of scorpion envenomation. Conclusion: While simultaneous administration of SAV and scorpion venom is effective in preventing scorpion envenomation-related manifestations, delayed administration of SAV, either at standard or elevated dosages, failed to alter any of

the scorpion envenomation features.
Descriptors: animal models, antivenoms, cardiac output, catecholamines, envenomation, epinephrine, haemodynamics, heart rate, laboratory animals, neuropeptides, norepinephrine, dogs, Scorpiones.

Foster, J.R. (2005). **Spontaneous and drug-induced hepatic pathology of the laboratory beagle dog, the cynomolgus macaque and the marmoset.** *Toxicologic Pathology* 33(1): 63-74. ISSN: 0192-6233.
Abstract: This review focuses on the background hepatic pathology present in three of the most commonly used species in the safety assessment of drugs, namely the beagle dog, the marmoset and the cynomolgus macaque. Both the nonneoplastic and neoplastic pathology are reviewed with a discussion on the potential impact that significant background pathology might have on the interpretation of any drug-induced pathology during subsequent testing. Although specific instances, such as parasitological infection in wild-caught primates can pose problems of interpretation, in general the background pathology in both the dog and the nonhuman primates, is not significantly different from that seen in the liver of laboratory rodents and with experience should not pose significant problems for the experienced pathologist. The relative merits of the primate versus the dog as a choice of second species are also considered in some detail. Although there is an inbuilt prejudice that the primate will more closely mimic subsequent effects that might occur in man in the clinic, insofar as the liver is concerned, there are many instances where the dog has been more representative of human exposure and metabolism and there is little evidence to show that the nonhuman primate is consistently better than dog in predicting human liver toxicity. As with most areas of science, comparative toxicology would dictate that the more information gained, from as wide a range of species as is practical, will give the best assessment for any subsequent problems in the clinic. This pragmatic approach should prove to be more successful than one based entirely upon an assumption, and in many cases the assumption is incorrect, that the primate always predicts human toxicity better than the nonprimate, including the dog.
Descriptors: callithrix physiology, liver diseases pathology, liver neoplasms, experimental chemically induced, liver neoplasms, experimental pathology, macaca fascicularis physiology, callithrix metabolism, metabolism, drug evaluation, preclinical, liver diseases genetics, liver neoplasms, experimental genetics, macaca fascicularis metabolism, models, animal, species specificity

Gamez, R., R. Mas, M. Noa, R. Menendez, H. Garcia, J. Gonzalez, Y. Perez, and E. Goicochea (2004). **Effects of chronic administration of d-003, a mixture of sugar cane wax high molecular acids, in beagle dogs**. *Drugs Under Experimental and Clinical Research* 30(2): 75-88. ISSN: 0378-6501.
Abstract: D-003 is a mixture of high molecular weight aliphatic primary acids purified from sugar cane wax (Saccharum officinarum, Q with cholesterol-lowering and antiplatelet effects. Previous studies, including a 6-month study conducted in rats, have shown no D-003-related toxicity. The present study was undertaken to investigate the effects of D-003 orally administered for 9 months in beagle dogs. The animals were randomly distributed in three groups: a control group receiving the vehicle only and two groups orally adminis-

tered D-003 (200 and 400 mg/kg). Body weight gain, food consumption and clinical signs were controlled throughout the study. The effects of D-003 on collagen-induced platelet aggregation, bleeding time (B T) and coagulation parameters (prothrombin time and kaolin-activated thromboplastin time) were also investigated. Most blood biochemistry and hematological parameters were assessed at baseline and after 6 and 9 months of treatment, while total cholesterol (TC), triglycerides, platelet aggregation, B T and coagulation parameters were determined at baseline and after 9 months of treatment. At study completion, the animals were sacrificed. D-003 at a dose of 200 and 400 mg/kg significantly reduced TC ($p < 0.05$), significantly inhibited platelet aggregation and increased BT compared with levels in controls. Data analyses of body weight gain, food consumption, clinical observations, the remaining blood biochemistry and hematology indicators (including coagulation parameters, organ weight ratios and histopathological findings) showed no trends with D-003 doses or significant differences between control animals and treated groups. In conclusion, D-003 administered for 9 months to beagle dogs induced the expected effects with no evidence of drug-related toxicity.
Descriptors: clinical chemistry, allied medical sciences, pharmacology, toxicology .

Han, J., J.C. Kim, M.K. Chung, B. Kim, and D.R. Choi (2003). **Subacute toxicity and toxicokinetics of a new antibiotic, dw-224a, after single and 4-week repeated oral administration in dogs.** *Biological and Pharmaceutical Bulletin* 26(6): 832-839. ISSN: 0918-6158.
NAL Call Number: QP501
Abstract: The subacute toxicity and toxicokinetics of a new fluoroquinolone antibiotic, DW-224a, were evaluated after single (on the 1st day) and 4-week (on the 28th day) oral administration of the drug at doses of 0 (to serve as a control), 10, 30, and 90 mg/kg/d, to male and female dogs (n = 3 for male and female dogs for each dose). During the test period, clinical signs, mortality, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, organ weight and histopathology were examined. The 4-week repeated oral dose of DW-224a resulted in vomiting, salivation, increased serum cholesterol level, and atrophy of thymus and testes. The target organ was determined to be the thymus and testes. The absolute toxic dose of DW-224a was 30 mg/kg and the level at which no adverse effects were observed was 10 mg/kg for both sexes. There were no significant gender differences in the pharmacokinetic parameters of DW-224a for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of DW-224a were dose independent after a single oral administration; the time to reach the peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentration-time curve from time zero to 24 h in plasma (AUC0-24 h) were not significantly different among the three doses. The accumulation of DW-224a after 4-week oral administration was not notable at the toxic dose of 90 mg/kg/d. For example, after 4-week administration, the dose-normalized AUC0-24 h value at 90 mg/kg/d (7.69, 7.05 mug h/ml) was not significantly greater than that at 10 mg/kg/d. After 4-week oral administration, the dose-normalized Cmax and AUC0-24 h at 90 mg/kg/d were not significantly higher and greater, respectively, than those after a single oral administration.
Descriptors: pharmacology, veterinary medicine, medical sciences, ophthalmoscopy, clinical techniques, therapeutic and prophylactic techniques, urinalysis, laboratory techniques.

Han, J., H.C. Shin, J.C. Kim, and B. Kim (2004). **Subacute toxicity and toxicokinetics of cj-10882, a type iv phosphodiesterase inhibitor, after 4-week repeated oral administration in dogs.** *Food and Chemical Toxicology* 42(3): 373-380. ISSN: 0278-6915.
NAL Call Number: 391.8 F73
Abstract: The subacute toxicity and toxicokinetics of a type IV phosphodiesterase inhibitor, CJ-10882, were evaluated after single (on the 1st day) and 4-week (on the 27th day) oral administration of the drug, in doses of 0 (to serve as a control), 2, 10 and 50 mg/kg/day, to male and female dogs (n=3 for male and female dogs for each dose). During the test period, clinical signs, mortality, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, organ weight and histopathology were examined. The 4-week repeated oral doses of CJ-10882 resulted in salivation, vomiting, and atrophy of the thymus. The absolute toxic dose was 50 mg/kg/day and the level at which no adverse effects were observed was 2 mg/kg/day for male and female dogs. There were no significant gender differences in the pharmacokinetic parameters of CJ-10882 for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of CJ-10882 were dose independent after a single oral administration; the time to reach a peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentration-time curve from time zero to 8 h in plasma (AUC0-8 h) were not significantly different among three doses. The accumulation of CJ-10882 after 4-week oral administration was not notable at the toxic dose of 50 mg/kg/day. For example, after 4-week administration, the dose-normalized AUC0-8 h value at 50 mg/kg/day (0.132 mug h/ml) was not significantly greater than that at 10 mg/kg/day (0.131 mug h/ml). After 4-week oral administration, the dose-normalized Cmax and AUC0-8 h at 50 mg/kg/day were not significantly higher and greater, respectively, than those after the single oral administration.
Descriptors: pharmacology, toxicology, salivation, vomiting.

Haushalter, T.M., G.S. Friedrichs, D.L. Reynolds, M. Barecki Roach, G. Pastino, R. Hayes, and A.S. Bass (2008). **The cardiovascular and pharmacokinetic profile of dofetilide in conscious telemetered beagle dogs and cynomolgus monkeys.** *British Journal of Pharmacology* 154(7): 1457-64. ISSN: 0007-1188.
NAL Call Number: 396.8 B77
Abstract: BACKGROUND AND PURPOSE: The effects of dofetilide were studied in monkeys and dogs. Pharmacokinetic data were generated together with the monitoring of cardiovascular changes in order to compare effects relative to human exposure. EXPERIMENTAL APPROACH: Beagle dogs and cynomolgus monkeys were telemetered to collect arterial blood pressure, heart rate and ECG for 6 h after selected oral doses of dofetilide. Pharmacokinetic parameters were determined for each dose. KEY RESULTS: Dogs: increases in the QT(c) interval reached 56 ms in dogs dosed with 0.3 mg kg(-1) of dofetilide. Premature ventricular contractions and right bundle branch block were evident at this dose, without changes in cardiovascular parameters. The mean C(max) values were 3.35 and 60.15 ng mL(-1) at doses of 0.03 and 0.3 mg kg(-1), respectively. Monkeys: increases in QT(c) intervals reached 40-50 ms after 0.03 mg kg(-1). T-wave changes were observed after 0.03 mg kg(-1) without changes in cardiovascular parameters. The mean C(max) values following oral doses of 0.01 and 0.03 mg kg(-1) were 0.919 ng mL(-1) and 1.85 ng mL(-1), respectively. CONCLUSIONS AND IMPLICATIONS: Despite dofetilide exposure comparable

to that in humans, QT(c) responses in dogs were greater than those reported in humans. A comparable human dose used in the monkey achieved only half of the exposure but was associated with twofold greater increases in QT(c). Our data support the view that safety risk assessments of new drugs in animal models should ensure that the clinical therapeutic range of exposure is achieved and any untoward effects interpreted accordingly.
Descriptors: anti arrhythmia agents toxicity, long qt syndrome chemically induced, models, animal, phenethylamines toxicity, sulfonamides toxicity, administration, oral, anti arrhythmia agents administration and dosage, anti arrhythmia agents pharmacokinetics, blood pressure drug effects, dogs, dose response relationship, drug, electrocardiography, heart rate drug effects, macaca fascicularis, phenethylamines administration and dosage, phenethylamines pharmacokinetics, species specificity, sulfonamides administration and dosage, sulfonamides pharmacokinetics, telemetry.

Horais, K., V. Hruby, S. Rossi, D. Cizkova, C. Meschter, R. Dorr, and T.L. Yaksh (2003). **Effects of chronic intrathecal infusion of a variant delta opioid agonist in dogs.** *Toxicological Sciences* 71(2): 263-275. ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Abstract: To define the effects of chronic spinal exposure to a highly selective variant delta opioid agonist c(DPen2,DPen5)enkephalin (DPDPE), adult beagles were prepared with chronic lumbar intrathecal catheters. Groups of dogs received intrathecal infusions (100 mul/h) of saline (vehicle), DPDPE 3 mg/ml or 6 mg/ml for 28 days. Over the 28-day period, saline or 3 mg/ml showed minimal changes in neurological function, whereas in the 6 mg/ml animals, prominent hind limb dysfunction evolved over the 28-day interval. Histopathology in control animals displayed a modest pericatheter reaction considered normal for this model. Dogs receiving DPDPE (three of four at 6 mg/ml and one of four at 3 mg/ml) but not saline (zero of four) developed large inflammatory masses (granulomas) in the intrathecal space located proximal to the catheter tip. In these masses, severe chronic inflammatory changes in combination with necrosis and fibrosis was detected. Occasional focal destruction of neuropil was detected also in the adjacent spinal cord parenchyma. These masses contained extensive accumulation of mouse antihuman macrophages (MAC)-positive inflammatory cells expressing tumor necrosis factor-alpha (TNF-alpha), revealing infiltration of macrophages, granulocytes, and monocytes. In separate animals, prepared with dual intrathecal catheters, lumbar CSF was sampled at specified time points following intrathecal bolus (3 mg/ml) and 24 h DPDPE infusion (3 mg/ml and 6 mg/ml). Steady-state cerebrospinal fluid (CSF) DPDPE levels were 18.6 +- 1.0 and 22.6 +- 4.0 mug/ml for 3 mg/ml and 6 mg/ml infusions respectively. These results indicate that this variant delta opioid agonist DPDPE produces a concentration and time-dependent formation of an intrathecal inflammatory mass.
Descriptors: neural coordination, pharmacology, toxicology, hind limb dysfunction, nervous system disease, toxicity, drug induced, intrathecal granuloma.

Javerliat, I., O. Goeau Brissonniere, P. Bruneval, and M. Coggia (2007). **Experimental study of a new vascular graft prebonded with antibiotic: healing, toxicity, and antibiotic retention.** *Annals of Vascular Surgery* 21(5): 603-10. ISSN: 0890-5096.
Abstract: Despite refinements in surgical techniques, routine antibioprophylaxis, and anesthesiology, vascular prosthetic infections remain a serious complication of reconstructive

vascular surgery. The purpose of this study was to evaluate the healing, the toxicity, and the antibiotic delivery of a new vascular graft, preloaded with rifampin and tobramycin. Sixteen dogs underwent infrarenal aortic bypass. They were divided into three groups. In test group 1 (n = 8), dogs received grafts loaded with a standard concentration of antibiotics. In test group 2 (n = 4), dogs received grafts loaded with twice the standard concentration of antibiotics. A control group (n = 4) received a commercial gelatin-sealed graft. Grafts were harvested after different periods of time and submitted to histological evaluation and antibiotic dose determination. Liver and kidney toxicities were evaluated from dosages performed on serum samples taken at different time periods between graft implantation and harvesting. The healing of antibiotic-loaded grafts was similar to that of commercial grafts, without any signs of toxicity. These results suggest resistance to infection of these prebonded grafts in an animal model.

Descriptors: anti bacterial agents administration and dosage, blood vessel prosthesis, prosthesis design, anti bacterial agents blood, anti bacterial agents chemistry, anti bacterial agents toxicity, aorta, abdominal pathology, aorta, abdominal surgery, biocompatible materials chemistry, dogs, gelatin chemistry, giant cells pathology, kidney drug effects, liver drug effects, models, animal, polyesters chemistry, prosthesis related infections prevention and control, rifampin administration and dosage, rifampin blood, rifampin chemistry, rifampin toxicity, surface properties, thrombosis pathology, time factors, tobramycin administration and dosage, tobramycin blood, tobramycin chemistry, tobramycin toxicity, tunica intima pathology, wound healing drug effects.

Kaluzienski, M. (2000). **Partial paralysis and altered behavior in dogs treated with melaleuca oil**. *Journal of Toxicology Clinical Toxicology* 38(5): 518-519. ISSN: 0731-3810.

NAL Call Number: RA1190.C5

Descriptors: biochemistry and molecular biophysics, veterinary medicine, medical sciences, toxicology, altered behavior, partial paralysis, meeting abstract

Kim, J.T., K.Y. Rhee, J.H. Bahk, S.H. Do, Y.J. Lim, H. Ko, and K.H. Lee (2003). **Continuous mixed venous oxygen saturation, not mean blood pressure, is associated with early bupivacaine cardiotoxicity in dogs.** *Canadian Journal of Anesthesia* 50(4): 376-381. ISSN: 0832-610X.

Abstract: Purpose: To investigate changes of continuous mixed venous oxygen saturation (cSvO2) and mean arterial blood pressure (MBP) in dogs with bupivacaine-induced cardiac depression. Methods: Bupivacaine was infused into pentobarbital-anesthetized mongrel dogs (n=8) at a rate of 0.5 mgcntdotkg-1cntdotmin-1 until the MBP was 40 mmHg or less (end of bupivacaine infusion; BIE). The infusion time was divided into the early period, first 30 min of bupivacaine infusion and the late period, which was from 30 min of bupivacaine infusion until BIE. cSvO2 was monitored using a fibreoptic pulmonary artery catheter, and MBP and cardiac output (CO) were measured every ten minutes after the initiation of bupivacaine infusion. Arterial blood gas, serum electrolyte and bupivacaine concentration were measured simultaneously. The relationships between CO and cSvO2, and of CO vs MBP were compared by regression analysis in the early and late periods. Results: The Pearson's correlation coefficients between CO and cSvO2 were 0.782 (P=2.1X10-7) in the early period and 0.824 (P=1.3X10-6) in the late period. The correlation coefficients between CO

and MBP were 0.019 (P=0.921) in the early period and 0.799 (P=4.8X10-6) in the late period. Conclusions: cSvO2, but not MBP, is associated with CO changes in bupivacaine-induced cardiac depression during the early period of bupivacaine intoxication. Decrease of MBP with low cSvO2 observed during the late period might imply severe cardiac depression induced by bupivacaine infusion.
Descriptors: cardiovascular system, transport and circulation, pharmacology, toxicology, bupivacaine induced cardiac depression, heart disease, toxicity, continuous mixed venous oxygen saturation, bupivacaine induced cardiotoxicity association, mean blood pressure.

Kimura, K., M. Tabo, K. Mizoguchi, A. Kato, M. Suzuki, Z. Itoh, S. Omura, and H. Takanashi (2007). **Hemodynamic and electrophysiological effects of mitemcinal (GM-611), a novel prokinetic agent derived from erythromycin in a halothane-anesthetized canine model.** *Journal of Toxicological Sciences* 32(3): 231-9. ISSN: 0388-1350.
NAL Call Number: RA1190
Abstract: Mitemcinal (GM-611) is a novel erythromycin-derived prokinetic agent that acts as an agonist at the motilin receptor. We investigated the QT-prolonging effects of mitemcinal using a halothane-anesthetized canine model. Intravenous administration of mitemcinal at doses of more than 8.3 mg/kg per 10 min significantly prolonged the QT interval corrected by Fridericia's corrections. Mitemcinal exhibited a bradycardiac effect and produced significantly greater prolongation in monophasic action potential duration (MAP(90)) at sinus rhythm compared with MAP(90) at pacing and showed reverse use-dependent prolongation of repolarization, suggesting that the negative chronotropic effect of mitemcinal potentiates the prolongation of the repolarization period. A technique using MAP/pacing electrodes allowed measurements of both MAP(90) and effective refractory period (ERP) simultaneously at the same ventricular site. Although mitemcinal slightly prolonged the MAP(90(CL400)) and ERP in comparison with the control group at the dose of 25 mg/kg per 10 min, the terminal repolarization period, the difference between MAP(90(CL400)) and ERP, did not increase suggesting the absence of a proarrhythmic effect even with a 7000-fold for the therapeutic blood concentration as free level. The electrophysiological results from mitemcinal in this study indicate that the risk of serious arrhythmia such as torsades de pointes, a major clinical concern related to QT interval prolongation, might be low.
Descriptors: blood pressure drug effects, erythromycin analogs and derivatives, gastrointestinal agents toxicity, gastrointestinal motility drug effects, heart rate drug effects, long qt syndrome chemically induced, torsades de pointes chemically induced, ventricular function, left drug effects, action potentials drug effects, anesthesia, general, anesthetics, inhalation, cardiac pacing, artificial, cisapride toxicity, dogs, dose response relationship, drug, electrocardiography, erythromycin administration and dosage, erythromycin blood, erythromycin toxicity, gastrointestinal agents administration and dosage, gastrointestinal agents blood, halothane, infusions, intravenous, long qt syndrome physiopathology, models, animal, risk assessment, time factors, torsades de pointes physiopathology, ventricular pressure drug effects.

Kling, D.E. and J.J. Schnitzer (2007). **Vitamin A deficiency (VAD), teratogenic, and surgical models of congenital diaphragmatic hernia (CDH).** *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 145c(2): 139-57. ISSN: 1552-4868.

Abstract: Congenital diaphragmatic hernia (CDH) is a congenital malformation that occurs with a frequency of 0.08 to 0.45 per 1,000 births. Children with CDH are born with the abdominal contents herniated through the diaphragm and exhibit an associated pulmonary hypoplasia which is frequently accompanied by severe morbidity and mortality. Although the etiology of CDH is largely unknown, considerable progress has been made in understanding its molecular mechanisms through the usage of genetic, teratogenic, and surgical models. The following review focuses on the teratogenic and surgical models of CDH and the possible molecular mechanisms of nitrofen (a diphenyl ether, formerly used as an herbicide) in both induction of CDH and pulmonary hypoplasia. In addition, the mechanisms of other compounds including several anti-inflammatory agents that have been linked to CDH will be discussed. Furthermore, this review will also explore the importance of vitamin A in lung and diaphragm development and the possible mechanisms of teratogen interference in vitamin A homeostasis. Continued exploration of these models will bring forth a clearer understanding of CDH and its molecular underpinnings, which will ultimately facilitate development of therapeutic strategies. (c) 2007 Wiley-Liss, Inc.
Descriptors: diaphragm embryology, hernia, diaphragmatic embryology, lung embryology, vitamin a physiology, vitamin a deficiency complications, disease models, animal, dogs, hernia, diaphragmatic chemically induced, hernia, diaphragmatic genetics, models, animal, phenyl ethers pharmacology, rabbits, rats, sheep, signal transduction, species specificity, teratogens pharmacology, tretinoin metabolism, vitamin a metabolism.

Mehta, A., A.C. Jain, and M.C. Mehta (2003). **Electrocardiographic effects of intravenous cocaine: an experimental study in a canine model.** *Journal of Cardiovascular Pharmacology* 41(1): 25-30. ISSN: 0160-2446.

Abstract: Cocaine abuse causes cardiac dysfunction. Acute intravenous administration of cocaine may lead to development of severe arrhythmias, conduction abnormalities, ST-T changes, and sudden death. Understanding arrhythmogenesis due to cocaine may provide a therapeutic approach to reduce morbidity and mortality. We studied the arrhythmogenic activity and other electrocardiographic abnormalities resulting from an intravenous bolus of cocaine. Baseline and postanesthetic electrocardiographic findings were compared with those after administration of intravenous bolus of various doses of cocaine hydrochloride in 20 dogs. The study was done in three phases (phase I: low dose of cocaine (1 mg/kg, 15 experiments); phase II: medium dose (2 mg/kg, 30 experiments); and phase III: high dose (5-7 mg/kg, 10 experiments)). Plasma levels of cocaine were estimated. The low dose induced sinus bradycardia, sinus arrhythmia, atrial ectopic, wandering pacemaker, unifocal ventricular premature contractions, and ventricular couplets. The medium dose generated moderately severe arrhythmias that were of supraventricular origin. Atrial flutter and atrial fibrillation were observed in two experiments each. Ventricular arrhythmias were manifested as unifocal, multifocal, interpolated ventricular premature contractions as well as bigeminy, trigeminy, couplets, and salvos. The high dose of 5-7 mg/kg increased electrocardiographic intervals and caused ST-segment elevation as well as serious life-threatening arrhythmias. Three of the dogs developed sustained ventricular tachycardia followed by ventricular flutter-fibrillation and death.
Descriptors: behavior, cardiovascular system, transport and circulation, toxicology, atrial ectopic, heart disease, atrial fibrillation, heart disease, atrial flutter, heart disease, cardiac

arrhythmia, drug abuse, behavioral and mental disorders, sinus arrhythmia, sinus bradycardia, ventricular tachycardia, st changes, unifocal ventricular premature contractions, ventricular couplets, wandering pacemaker.

Mirsalis, J.C., J. Schindler Horvat, J.R. Hill, C.E. Green, C. Mitoma, J.E. Tomaszewski, C.A. Tyson, and S.J. Donohue (2003). **Toxicity of a quinocarmycin analog, dx-52-1, in rats and dogs in relation to clinical outcome.** *Cancer Chemotherapy and Pharmacology* 51(3): 193-201. ISSN: 0344-5704.

NAL Call Number: RC271.C5C28

Abstract: Purpose: Quinocarmycin analog DX-52-1 is a cyanated derivative of quinocarmycin, a compound isolated from cultures of Streptomyces melanovinaceus. DX-52-1 was selected for preclinical development because it showed efficacy against melanoma cell lines in the NCI human tumor cell screen and melanoma xenografts in mice. This report describes studies in rats and dogs to determine the maximum tolerated dose (MTD) and identify dose-limiting toxicities (DLT) in each species in different regimens to establish a safe starting dose and potential target organs of DX-52-1 for phase I clinical trials. Methods: DX-52-1 was administered to Fischer 344 rats using repeated intravenous (i.v.) slow bolus injections following q3hX3 and q3hX3,q7dX3 regimens, and to beagle dogs using a single injection, 6-h continuous i.v. infusion (c.i.v.) and weekly 6-h c.i.v. for 3 weeks. Endpoints evaluated included clinical observations, body weights, hematology, serum clinical chemistry, and microscopic pathology of tissues. Results: The MTD of DX-52-1 was a total dose of 18 mg/m2 body surface area for q3hX3 administration in rats and 30 mg/m2 for a single c.i.v. administration in dogs. The total dose MTD for rats on a weekly (q3hX3,q7dX3) regimen was 54 mg/m2, and for dogs on the weekly X3 (6-h c.i.v.) infusion was 60 mg/m2. In rats, significant elevations in blood urea nitrogen and creatinine were observed together with acute renal tubular necrosis histologically. Modest increases in liver enzymes were also observed, as were decreases in reticulocytes that were unaccompanied by histologic changes in liver and bone marrow. In dogs, adverse signs included vomiting/retching, diarrhea, and transient hypothermia; also red blood cells, hemoglobin, hematocrit, and lymphocytes were decreased. Histologic evaluation of tissues from dogs revealed necrosis and cellular depletion of the bone marrow, and extensive damage to the entire gastrointestinal tract, including marked cellular necrosis of the mucosa and lymphoid necrosis of the gastrointestinal associated lymphoid tissue. Destruction of the mucosal lining of the intestinal tract was likely responsible for dehydration, toxemia, septicemia, and shock seen in moribund dogs. Conclusions: The MTD values were comparable between rats and dogs given roughly similar dose regimens (single dose or weekly) and both species tolerated a higher total dose with weekly administration. However, the principal target organ responsible for DLT in rats was the kidney, whereas in dogs, the most severe effects were on the gastrointestinal tract and bone marrow. Both renal and gastrointestinal toxicities were reported in patients after 6-h c.i.v. infusions in a limited phase I clinical trial, indicating that neither animal model alone was predictive of DX-52-1-induced toxicity in humans, and that both species were required to define human toxicity.

Descriptors: animal models, rats, dogs, human, cancer therapy, melanoma, toxicity studies, preclinical development, Quinocarmycin analog DX-52-1, efficacy pharmacology, toxicology, bone marrow toxicity, blood and lymphatic disease, gastrointestinal toxicity, digestive system

disease, renal toxicity, toxicity, urologic disease, histopathology, histology and cytology techniques, laboratory techniques, body weight, species differences.

Mueller, T., B. Van-De-Sluis, A. Zhernakova, E. Van-Binsbergen, A.-R. Janecke, A. Bavdekar, A. Pandit, H. Weirich-Schwaiger, H. Witt, H. Ellemunter, J. Deutsch, H. Denk, W. Mueller, I. Sternlieb, M.-S. Tanner, and C. Wijmenga (2003). **The canine copper toxicosis gene murr1 does not cause non-wilsonian hepatic copper toxicosis.** *Journal of Hepatology* 38(2): 164-168. ISSN: 0168-8278.

NAL Call Number: RC845

Abstract: Background: Non-Wilsonian hepatic copper toxicosis includes Indian childhood cirrhosis (ICC), endemic Tyrolean infantile cirrhosis (ETIC) and the non-Indian disease known as idiopathic copper toxicosis (ICT). These entities resemble the hepatic copper overload observed in livers of Bedlington terriers with respect to their clinical presentation and biochemical and histological findings. We recently cloned the gene causing copper toxicosis in Bedlington terriers, MURR1, as well as the orthologous human gene on chromosome 2p13-p16. Aim: To study the human orthologue of the canine copper toxicosis gene as a candidate gene for ICC, ETIC, and ICT. Methods: We sequenced the exons and the intron-exon boundaries of the human MURR1 gene in 12 patients with classical ICC, one patient with ETIC, and 10 patients with ICT to see whether these patients display any mutations in the human orthologue of the canine copper toxicosis gene. Results: No mutations in the MURR1 gene, including the intron-exon boundaries, were identified in a total of 23 patients with non-Wilsonian hepatic copper toxicosis. Conclusions: Our results demonstrate that copper toxicosis in Bedlington terriers is not an animal model for the non-Wilsonian hepatic copper toxicosis described in this study.

Descriptors: gastroenterology, human medicine, medical sciences, molecular genetics, biochemistry and molecular biophysics, toxicology, Indian childhood cirrhosis, digestive system disease, etiology, endemic Tyrolean infantile cirrhosis, idiopathic copper toxicosis, metabolic disease, toxicity, etiology, non Wilsonian hepatic copper toxicosis, metabolic disease, toxicity, pathology, clinical presentation.

Nair, B. and A.R. Elmore (2003). **Final report on the safety assessment of sodium sulfite, potassium sulfite, ammonium sulfite, sodium bisulfite, ammonium bisulfite, sodium metabisulfite and potassium metabisulfite.** *International Journal of Toxicology* 22(Supplement 2): 63-88. ISSN: 1091-5818.

NAL Call Number: RA1190.J61

Abstract: Sodium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Potassium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are inorganic salts that function as reducing agents in cosmetic formulations. All except Sodium Metabisulfite also function as hair-waving/straightening agents. In addition, Sodium Sulfite, Potassium Sulfite, Sodium Bisulfite, and Sodium Metabisulfite function as antioxidants. Although Ammonium Sulfite is not in current use, the others are widely used in hair care products. Sulfites that enter mammals via ingestion, inhalation, or injection are metabolized by sulfite oxidase to sulfate. In oral-dose animal toxicity studies, hyperplastic changes in the gastric mucosa were the most common findings at high doses. Ammonium Sulfite aerosol had an acute LC50 of >400 mg/m3 in guinea pigs. A single exposure to low concentrations of a Sodium Sulfite

fine aerosol produced dose-related changes in the lung capacity parameters of guinea pigs. A 3-day exposure of rats to a Sodium Sulfite fine aerosol produced mild pulmonary edema and irritation of the tracheal epithelium. Severe epithelial changes were observed in dogs exposed for 290 days to 1 mg/m3 of a Sodium Metabisulfite fine aerosol. These fine aerosols contained fine respirable particle sizes that are not found in cosmetic aerosols or pump sprays. None of the cosmetic product types, however, in which these ingredients are used are aerosolized. Sodium Bisulfite (tested at 38%) and Sodium Metabisulfite (undiluted) were not irritants to rabbits following occlusive exposures. Sodium Metabisulfite (tested at 50%) was irritating to guinea pigs following repeated exposure. In rats, Sodium Sulfite heptahydrate at large doses (up to 3.3 g/kg) produced fetal toxicity but not teratogenicity. Sodium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite were not teratogenic for mice, rats, hamsters, or rabbits at doses up to 160 mg/kg. Generally, Sodium Sulfite, Sodium Metabisulfite, and Potassium Metabisulfite were negative in mutagenicity studies. Sodium Bisulfite produced both positive and negative results. Clinical oral and ocular-exposure studies reported no adverse effects. Sodium Sulfite was not irritating or sensitizing in clinical tests. These ingredients, however, may produce positive reactions in dermatologic patients under patch test. In evaluating the positive genotoxicity data found with Sodium Bisulfite, the equilibrium chemistry of sulfurous acid, sulfur dioxide, bisulfite, sulfite, and metabisulfite was considered. This information, however, suggests that some bisulfite may have been present in genotoxicity tests involving the other ingredients and vice versa. On that basis, the genotoxicity data did not give a clear, consistent picture. In cosmetics, however, the bisulfite form is used at very low concentrations (0.03% to 0.7%) in most products except wave sets. In wave sets, the pH ranges from 8 to 9 where the sulfite form would predominate. Skin penetration would be low due to the highly charged nature of these particles and any sulfite that did penetrate would be converted to sulfate by the enzyme sulfate oxidase. As used in cosmetics, therefore, these ingredients would not present a genotoxicity risk. The Cosmetic Ingredient Review Expert Panel concluded that Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite are safe as used in cosmetic formulations.
Descriptors: cosmetics, toxicology, pulmonary edema, respiratory system disease, oral dose animal toxicity test, laboratory techniques, genotoxicity data, lung capacity parameters, pH, skin penetration.

Quimby, F.W., A.C. Casey, and M.F. Arquette (2005). **From dogs to frogs: how pets, laboratory animals, and wildlife aided in elucidating harmful effects arising from a hazardous dumpsite.** *ILAR Journal* 46(4): 364-9. ISSN: 1084-2020.
NAL Call Number: QL55.A1I43
Abstract: The medical literature contains many examples of cases in which serendipitous observations have led to important findings. In the example described in this article, laboratory and field observations conducted at the Mohawk Nation Community of Akwesasne led to the important and unexpected finding that frogs once plentiful in the area were no longer observed. Laboratory tests comparing river sediments from Akwesasne to pristine sediment from Ithaca, NewYork, indicated multiple adverse health effects on developing frogs. Some of the behavioral changes observed in the laboratory were similar to those described by residents of Akwesasne before the onset of amphibian decline. The magnitude of changes paralleled

frog body burden of polychlorinated biphenyls acquired from the Akwesasne sediment. The impact of these findings on the identification of a hazardous waste site and global amphibian decline are discussed.
Descriptors: environmental exposure adverse effects, hazardous waste adverse effects, polychlorinated biphenyls blood, water pollutants, chemical blood, amphibia, animals, domestic, animals, laboratory, animals, wild, birds, dogs, indians, north american, new york, rats, rivers

Ridgway, P., T.E. Nixon, and J.P. Leach (2003). **Occupational exposure to organic solvents and long-term nervous system damage detectable by brain imaging, neurophysiology or histopathology.** *Food and Chemical Toxicology* 41(2): 153-187. ISSN: 0278-6915.
NAL Call Number: 391.8 F73
Abstract: The purpose of the present review is to assess the evidence published in scientific literature that industrial organic solvents as a generic group have the ability to induce long-term nervous system damage in workers that can be detected by techniques other than neuropsychological testing. The main body of evidence considered in this review was 40 studies involving the use of brain imaging, neurophysiological testing, gross autopsy or histopathology in groups of workers with long-term solvent exposure. Case reports involving both solvent abuse and occupational exposure, and experimental animal data have also been reviewed as supporting data. A number of the studies in groups of workers provide evidence of the presence of marginal atrophic abnormalities in the brain or deficits in nerve conduction velocity in solvent-exposed workers. However, there are limitations in the design of many of these studies, the strength of association between exposure and effect is not consistently strong, no dose-response relationship can be detected, the reported changes lack specificity and there is no coherence between the human and experimental animal data. Overall, it is not possible to draw reliable conclusions with respect to the presence or absence of nervous system damage related to the common properties of organic solvents.
Descriptors: nervous system, neural coordination, toxicology, organic solvent abuse, brain imaging, imaging, microscopy techniques, laboratory techniques, gross autopsy, histopathology, cytology techniques .

Sattler-J , Hesterberg-R , Lorenz-W , Schmidt-U , Crombach-M , and Stahlknecht-C-D (1985). **Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit relevance for clinical side effects.** *Agents and Actions* 16(3-4): 91-94. ISSN: 0065-4299.
Descriptors: enzymology, biochemistry and molecular biophysics, metabolism , pharmacology, toxicology, neuromuscular blocking drugs, cephalosporins, histamine levels.

Schaefer, G.J., D.T. Kirkpatrick, J.F. Holson, C.P. Chengelis, K.S. Regan, and V.J. Piccirillo (2003). **A six-week inhalation neurotoxicity study of methyl bromide in dogs.** *Toxicological Sciences* 72(S-1): 304 ISSN: 1096-6080.
NAL Call Number: RA1190.F8
Descriptors: nervous system, neural coordination, toxicology, locomotor activity.

Stonerook, M., C. Hassler, P. Tosca, J. Merrill, D. Vasconcelos, and A. Smith (2003). **Cardiotoxicity study of nsc-638850 (ucn-01) and cytostar (ara-c) given alone or in combination to beagle dogs.** *Toxicological Sciences* 72(S-1): 36 ISSN: 1096-6080.

NAL Call Number: RA1190.F8
Descriptors: pharmacology, toxicology, cardiotoxicity, heart disease, toxicity, drug induced, ecg, electrocardiography, clinical techniques, diagnostic techniques, cardiovascular evaluation, combination chemotherapy, therapeutic and prophylactic techniques, blood pressure, body temperature, heart rate, necrosis, vascular resistance, venodilation .

Stump, D.G., J.F. Holson, L.B. Pearce, V.T. Rentko, and M.S. Gawryl (2003). **Finding of developmental toxicity studies of hboc-201 in rodent and canine models.** *Birth Defects Research* 68(3): 250. ISSN: 1542-0752.
NAL Call Number: QL991 .T4
Descriptors: development, pharmacology, toxicology .

Sztajnkrycer, M.D., G.R. Bond, S.B. Johnson, and A.L. Weaver (2004). **Use of vasopressin in a canine model of severe verapamil poisoning: a preliminary descriptive study.** *Academic Emergency Medicine* 11(12): 1253-61. ISSN: 1069-6563.
Abstract: OBJECTIVES: The purpose of this preliminary study was to evaluate the effect of arginine vasopressin (AVP) administration in a model of shock induced by calcium channel antagonist overdose and to determine endogenous serum AVP concentrations in calcium channel antagonist-induced shock. METHODS: This was a controlled, randomized laboratory investigation based on a previously described canine model of verapamil toxicity. After induction of verapamil toxicity, animals in both the control and the experimental groups (n = 6 each) received a continuous infusion of verapamil. Experimental animals received an escalating dose of AVP, while control animals received an equal volume of 0.9% saline infusion. The hemodynamic end point was return of mean arterial pressure (MAP) to within 20% of baseline. Surviving animals were killed after 60 minutes. RESULTS: In the treatment group, administration of low-dose AVP (4 mU/kg/min) resulted in further declines in cardiac index and heart rate. No significant change was noted in MAP with low-dose AVP. A slight increase in MAP was noted with both escalating doses of AVP and equivalent volumes of normal saline. By the end of the 60-minute antidote/saline phase, the MAPs of the saline control group and the AVP experimental group were similar. The primary hemodynamic end point was not achieved in either the AVP or the saline control arm. Mean baseline serum AVP concentration in control animals was 5.8 pg/mL, increasing to 225 pg/mL during the toxicity phase. CONCLUSIONS: In an animal model of verapamil-induced shock, endogenous AVP levels increased nearly 40-fold compared with baseline levels. Escalating doses of exogenous AVP worsened cardiac index and failed to return MAP to within 20% of baseline.
Descriptors: animal model, induced shock, calcium channel antagonist overdose. toxicity, cadiac index.

Tarasiuk, A., T. Ahmad, and S. Sofer (2002). **Volume resuscitation does not alleviate peripheral organ ischemia in dogs injected with scorpion venom**. *Critical Care Medicine.* 30(7): 1581-1588. ISSN: 0090-3493.
Abstract: Objectives: To examine the effect of fluid resuscitation on the haemodynamic changes in dogs injected with scorpion venom and to explore the effects of the venom on the determinants of venous return (i.e., circulatory compliance, time constant, and resistance to venous return). Design: A prospective, controlled animal study. Setting: University animal

research laboratory. Subjects: Mixed-breed dogs. Interventions: The effect of volume resuscitation (20 ml/kg of the synthetic colloid polygeline) 1 hr after venom injection (a time previously found to be related to severe decrease in cardiac output) was tested in two series of experiments. In the first series, 12 dogs were given venom and fluid, eight dogs were given venom alone, and four dogs served as the time-controlled group. In the second series, eight dogs were given venom and ten dogs served as controls. Scorpion venom (Leiurus quinquestriatus) at 0.1 mg/kg in the first series and 0.05 mg/kg in the second series was given intravenously. Measurements and Main Results: In the first series of experiments, the venom decreased cardiac output from 5.0+or-1.1 to 2.9+or-0.7 litres/min at 60 mins (p<.001). Arterial pH decreased from 7.39+or-0.05 to 7.16+or-0.1 (p<.001). Blood lactate increased from 0.9+or-0.8 to 3.2+or-1.9 mM (p<.05). Gastric pH decreased from 7.28+or-0.2 to 6.7+or-0.18 (p<.001). Arterial acidosis was secondary to gastrointestinal ischaemia because the gradient between mucosal and arterial PCO2 increased from 17.5+or-7.7 to 98.6+or-75 (p<.01) 60 mins after venom injection. In the second series of experiments, circulatory compliance and time constant increased by 150% and 128%, respectively (p<.05), in dogs injected with venom compared with control dogs. Resistance to venous return increased after venom injection but did not change after fluid infusion. In both series of experiments, volume administration improved cardiac output but had no effect on oxygen delivery, arterial pH, HC03-, lactate, and gastric mucosal pH. Conclusions: Metabolic acidosis and cardiovascular abnormalities seen after scorpion venom injection in dogs are closely related to gastrointestinal hypoperfusion. Fluid resuscitation increased cardiac output but had no effect on gastrointestinal perfusion and acidosis induced by the venom.
Descriptors: scorpion venom , Leiurus quinquestriatus, blood pressure, hemodynamics, heart rate, ischemia, fluid resuscitation, metabolic acidosis, cardiovascular abnormalities.

Tarasiuk, A., S. Khvatskin, and S. Sofer (1998). **Effects of antivenom serotherapy on hemodynamic pathophysiology in dogs injected with L. quinquestriatus scorpion venom**. *Toxicon* 36(7): 963-971. ISSN: 0041-0101.
NAL Call Number: 391.8 T66
Abstract: In dogs, scorpion venom causes an immediate increase in cardiac output that declines below baseline values within 1 h. The hypotheses that antivenom given before venom injection may prevent changes in cardiac output, while antivenom given after the inotropic stage of envenomation cannot reverse cardiac output decline were tested. 25 anaesthetized, mechanically ventilated dogs were given 0.1 mg/kg IV venom of the scorpion Leiurus quinquestriatus. The dogs were randomized into 4 groups: 5 dogs were given venom alone (control group) and 6 dogs were given 6 ml of antivenom 1 minute before venom injection while 8 and 6 dogs were given 6 ml of antivenom 20 and 60 min after venom injection, respectively. Parameters reflecting respiratory and circulatory functions were measured for 180 min after venom injection. Scorpion venom caused a gradual decrease in heart rate, an initial elevation of systemic and pulmonary blood pressure and cardiac output followed by a decline in these parameters. PO2, pH and HCO3- gradually decreased, while PCO2 gradually increased from baseline. Antivenom given before venom injection prevented all the effects induced by the venom. Antivenom given at 20 and 60 min after venom injection had no effect on cardiac output and HCO3- decline, but caused an increase in heart rate, PO2 and pH and a decrease in PCO2. It is assumed that antivenom clears free toxins from

the circulation, and since cardiac output and HCO3- did not improve after this clearance, it is concluded that following intravenous venom injection, heart and circulation are rapidly affected by the toxins or by other substances released by the venom which do not respond to antivenom. Improvements in respiration and heart rate with antivenom given after venom injection may be secondary to reversion of cholinergic effects of the venom. Improvement in respiration may be also explained by reversion of the toxic effects on Ca2+ activated K+ channels of bronchial smooth muscle. All these effects may be secondary to clearance of toxins by the antivenom.

Descriptors: physiopathology, venoms, heart, antivenoms, laboratory animals, laboratory mammals, blood pressure, envenomation, toxins, pH, blood analysis, smooth muscle, calcium ions, dogs, Leiurus quinquestriatus, Arachnida.

Tarasiuk, A., S. Menascu, and S. Sofer (2003). **Antivenom serotherapy and volume resuscitation partially improve peripheral organ ischemia in dogs injected with scorpion venom**. *Toxicon* 42(1): 73-77. ISSN: 0041-0101.

NAL Call Number: 391.8 T66

Abstract: We tested the hypothesis that fluid resuscitation combined with antivenom serotherapy given after injection of scorpion venom may increase cardiac output (CO) and blood pressure (BP) and prevent the decline in bicarbonate, pH and gastric perfusion. Seventeen anesthetized, mechanically ventilated dogs were given 0.1 mg/kg IV venom of the scorpion Leiurus quinquestriatus. The dogs were randomized into three groups: six dogs were given venom alone; three dogs were given 6 ml of antivenom 1 minute before venom injection; eight dogs were given 6 ml of antivenom and 20 ml/kg of synthetic colloid solution, 20 min after venom injection. Parameters reflecting respiratory and circulatory functions were determined at baseline and 120 min after venom injection. Scorpion venom caused a decrease in CO, BP, pH and HCO3-. Gastric mucosal perfusion was severely affected as assessed by mucosal pH (pHi) and the gradient between mucosal and arterial pCO2 (Delta pCO2). Antivenom given before venom injection prevented all the effects induced by the venom. Antivenom and fluid given 20 min after venom injection caused a marked increase in CO and BP, but had no effect on pH and HCO3- decline (compared with venom alone). Gastric perfusion slightly improved as the increase in Delta pCO2 was attenuated. The combination therapy of antivenom and fluid in this dog model is superior to the therapy of each of them alone. The marked and long-standing improvement of CO is promising and may suggest improvement in HCO3- and pH with time.

Descriptors: animal models, antivenoms, blood flow, blood pressure, cardiac output, drug therapy, envenomation, fluid therapy, ischaemia, laboratory animals, stomach mucosa, venoms, dogs, Leiurus quinquestriatus.

Tarasiuk, A., A. Taya, and S. Sofer (2002). **Volume resuscitation does not alleviate peripheral organ ischemia in dogs injected with scorpion venom.** *Critical Care Medicine.* 30(7): 1581-8. ISSN: 0090-3493.

Abstract: OBJECTIVES: To examine the effect of fluid resuscitation on the hemodynamic changes in dogs injected with scorpion venom and to explore the effects of the venom on the determinants of venous return (i.e., circulatory compliance, time constant, and resistance to venous return). DESIGN: A prospective, controlled animal study. SETTING: University

animal research laboratory. SUBJECTS: Mixed-breed dogs. INTERVENTIONS: The effect of volume resuscitation (20 mL/kg of the synthetic colloid polygeline) 1 hr after venom injection (a time previously found to be related to severe decrease in cardiac output) was tested in two series of experiments. In the first series, 12 dogs were given venom and fluid, eight dogs were given venom alone, and four dogs served as the time-controlled group. In the second series, eight dogs were given venom and ten dogs served as controls. Scorpion venom (Leiurus quinquestriatus) at 0.1 mg/kg in the first series and 0.05 mg/kg in the second series was given intravenously. MEASUREMENTS AND MAIN RESULTS: In the first series of experiments, the venom decreased cardiac output from 5.0 +/- 1.1 to 2.9 +/- 0.7 L/min at 60 mins (p <.001). Arterial pH decreased from 7.39 +/- 0.05 to 7.16 +/- 0.1 (p <.001). Blood lactate increased from 0.9 +/- 0.8 to 3.2 +/- 1.9 mM (p <.05). Gastric pH decreased from 7.28 +/- 0.2 to 6.7 +/- 0.18 (p <.001). Arterial acidosis was secondary to gastrointestinal ischemia because the gradient between mucosal and arterial Pco2 increased from 17.5 +/- 7.7 to 98.6 +/- 75 (p <.01) 60 mins after venom injection. In the second series of experiments, circulatory compliance and time constant increased by 150% and 128%, respectively (p <.05), in dogs injected with venom compared with control dogs. Resistance to venous return increased after venom injection but did not change after fluid infusion. In both series of experiments, volume administration improved cardiac output but had no effect on oxygen delivery, arterial pH, HCO3-, lactate, and gastric mucosal pH. CONCLUSIONS: Metabolic acidosis and cardiovascular abnormalities seen after scorpion venom injection in dogs are closely related to gastrointestinal hypoperfusion. Fluid resuscitation increased cardiac output but had no effect on gastrointestinal perfusion and acidosis induced by the venom.
Descriptors: scorpion venom, toxicity, fluid resuscitation, hemodynamic changes, metabolic acidosis, gastrointestinal hypoperfusion.

Tegzes, J.H., S.D. Smarick, and B. Puschner (2002). **Coma and apnea in a dog with hydroxyzine toxicosis.** *Veterinary and Human Toxicology* 44(1): 24-6. ISSN: 0145-6296.
NAL Call Number: SF601.A47
Abstract: Hydroxyzine is a commonly prescribed H1-receptor antagonist in small animal practice. The most common adverse effect reported after therapeutic dosing is mild sedation; severe reactions resulting in coma have occasionally been reported in children. We present a case of large po hydroxyzine exposure causing in coma and apnea in a dog. Exposure was confirmed with gas chromatography/mass spectrometry analysis of urine. Extensive therapeutic measures to enhance drug elimination and assist ventilation were required for 11 d. The positive outcome justifies critical care of similarly exposed animals. Veterinarians should be aware of the potential for coma and apnea secondary to hydroxyzine exposure.
Descriptors: hydroxyzine, H1-receptor antagonist, poisoning, toxicology, sedation, coma.

Teo, S.K., D.I. Stirling, S.D. Thomas, M.G. Evans, and V.D. Khetani (2003). **A 90-day oral gavage toxicity study of d-methylphenidate and d,l-methylphenidate in beagle dogs.** *International Journal of Toxicology* 22(3): 215-226. ISSN: 1091-5818.
NAL Call Number: RA1190.J61
Abstract: d-Methylphenidate (d-MPH) was approved as a treatment for attention deficit hyperactivity disorder (ADHD) in children. The repeated-dose toxicity of the d enantiomer of d,l-methylphenidate (d,l-MPH) was assessed in male and female Beagle dogs. Dogs were

orally dosed twice a day in equally divided doses 6 hours apart for total daily doses of 1, 3, and 10 mg/kg/day d-MPH or 20 mg/kg/day d,l-MPH for 90 days, followed by a 30-day recovery period. The top d-MPH dose of 10 mg/kg was equimolar to 20 mg/kg d,l-MPH in d-MPH content. The 10-mg/kg d-MPH and d,l-MPH doses were at least 13 times the maximum therapeutic dose giving rise to systemic exposures that were equivalent to or at least 2 times greater than those at the maximum therapeutic doses in children. The 10-mg/kg d-MPH and 20-mg/kg d,l-MPH doses had systemic exposures that were equivalent to or two to five times greater than the maximum therapeutic plasma levels in children respectively. There was no treatment-related mortality in all doses tested. Reversible salivation, hyperactivity, and diarrhea were seen in the high-dose d-MPH and d,l-MPH groups. Significant body weight loss and reduction in food consumption were observed in males for both high-dose groups with weights comparable to control values by the end of the recovery period. There were no abnormal clinical pathology or macroscopic or microscopic findings. Based on body weight changes, the no-observed-adverse-effect level (NOAEL) of d-MPH in beagle dogs was 3 mg/kg/day.

Descriptors: pharmacology, toxicology, veterinary medicine, medical sciences, attention deficit hyperactivity disorder, ADHD, (Attention Deficit Disorder with Hyperactivity), behavioral and mental disorders, digestive system disease, oral gavage toxicity study, clinical techniques, body weight loss, food consumption.

Tontodonati, M., N. Fasdelli, E. Moscardo, A. Giarola, and R. Dorigatti (2007). **A canine model used to simultaneously assess potential neurobehavioural and cardiovascular effects of candidate drugs.** *Journal of Pharmacological and Toxicological Methods* 56(2): 265-75. ISSN: 1056-8719.

NAL Call Number: QP901.J6

Abstract: INTRODUCTION: Unwanted effects of drugs on neurobehavioural and cardiovascular functions are normally assessed in separate studies and using different animals. A new model using dogs which allows for the integration of these assessments into a single study was established and validated, adopting the most sophisticated technologies for both monitoring behaviour by video recordings and cardiovascular parameters by telemetry. METHODS: Conscious male beagle dogs (n=4) were given single oral doses of vehicle, and D-amphetamine (0.25, 0.75, 1.5 mg/kg) or acepromazine (0.05, 0.3, 2 mg/kg) within two different studies. Blood pressure, heart rate, electrocardiogram (EKG), body temperature, motor activity and behaviour (by video) were monitored continuously for 24 h post-dose. Animals underwent a full neurobehavioural examination the day before dosing, at the time to the maximal plasma concentration (Tmax) and 24 h post-dose. RESULTS: D-Amphetamine: a dose-dependent increase in arterial blood pressure was noted at all doses and was generally associated with an increase in the QA interval, an index of cardiac contractility. Heart rate also increased but only at the 1.5 mg/kg dose. A dose-dependent general excitatory state of the nervous system was observed, characterised mainly by hyper-reactivity, and stereotyped activities. Acepromazine: a decrease in systolic blood pressure was detected at 0.3 and 2 mg/kg generally associated with a decrease in pulse pressure reflecting a negative inotropic effect. A dose-related increase in heart rate accompanied this effect. Dose-dependent general depression of the nervous system was noted; mainly characterised by half-closed eyes, subdued behaviour and impaired posture. In both studies, all dogs completely recovered at

approximately 16 h after treatment. DISCUSSION: Cardiovascular and neurobehavioural changes expected from the pharmacology of test substances were accurately detected. No significant fluctuations of the telemetric parameters recorded were noted as a consequence of the handling associated with the direct neurobehavioural examination. These results confirm the validity of this combined model capable of providing a reliable neurobehavioural and cardiovascular assessment of drugs.

Descriptors: behavior, animal drug effects, cardiovascular physiological phenomena drug effects, drugs, investigational pharmacology, models, animal, acepromazine administration and dosage, acepromazine pharmacology, acepromazine toxicity, administration, oral, behavior, animal physiology, blood pressure drug effects, body temperature drug effects, body temperature physiology, dextroamphetamine administration and dosage, dextroamphetamine pharmacology, dextroamphetamine toxicity, dogs, dose response relationship, drug, drugs, investigational administration and dosage, drugs, investigational toxicity, electrocardiography drug effects, electrocardiography methods, heart rate drug effects, hyperkinesis chemically induced, hyperkinesis physiopathology, hypnotics and sedatives administration and dosage, hypnotics and sedatives pharmacology, hypnotics and sedatives toxicity, long qt syndrome chemically induced, long qt syndrome physiopathology, motor activity drug effects, motor activity physiology, reflex, pupillary drug effects, reflex, pupillary physiology, reproducibility of results, sialorrhea chemically induced, sialorrhea physiopathology, telemetry methods.

Trepanier, L.A. (2004). **Idiosyncratic toxicity associated with potentiated sulfonamides in the dog**. *Journal of Veterinary Pharmacology and Therapeutics* 27(3): 129-138. ISSN: 0140-7783.

NAL Call Number: SF915.J63

Abstract: Idiosyncratic toxicity to potentiated sulfonamides occurs in both humans and dogs, with considerable clinical similarities. The syndrome in dogs can consist of fever, arthropathy, blood dyscrasias (neutropenia, thrombocytopenia, or hemolytic anemia), hepatopathy consisting of cholestasis or necrosis, skin eruptions, uveitis, or keratoconjunctivitis sicca. Other manifestations seen less commonly include protein-losing nephropathy, meningitis, pancreatitis, pneumonitis, or facial nerve palsy. The pathogenesis of these reactions is not completely understood, but may be due to a T-cell-mediated response to proteins haptenated by oxidative sulfonamide metabolites. Our laboratory is working on tests to characterize dogs with possible idiosyncratic sulfonamide reactions, to include ELISA for anti-drug antibodies, immunoblotting for antibodies directed against liver proteins, flow cytometry for drug-dependent anti-platelet antibodies, and in vitro cytotoxicity assays. The management of idiosyncratic sulfonamide toxicity involves client education to identify clinical signs early and allow rapid drug discontinuation, supportive care to include possibly ascorbate and glutathione precursors, and avoidance of subsequent re-exposure. It is important to realize that only antimicrobial sulfonamides, such as sulfamethoxazole, sulfadiazine, and sulfadimethoxine, share this clinical syndrome. There is no evidence for cross-reactivity with drugs that have different underlying structures but share a sulfonamide moiety, such as acetazolamide, furosemide, glipizide, or hydrochlorothiazide.

Descriptors: adverse effects, antibodies, clinical aspects, dosage effects, drug allergies, drug toxicity, pathogenesis, reviews, sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfonamides, T lymphocytes, treatment, pharmacology, elisa, immunologic techniques, laboratory techniques, cytotoxicity assay, bioassay techniques, flow cytometry.

Weekley, L.B., P. Guittin, and G. Chamberland (2002). **The international symposium on regulatory testing and animal welfare: recommendations on best scientific practices for safety evaluation using nonrodent species.** *ILAR Journal* 43 Suppl: S118-22. ISSN: 1084-2020.
NAL Call Number: QL55.A1I43
Descriptors: toxicity testing, toxicological studies, safety evaluation, data collection, dose selection, repeat dose exposure, blood collection, euthanasia, dog, monkey, minature swine.

Wight, S. (2004). **Benefits of 24-hour food access for dogs on toxicology studies**. *Animal Technology and Welfare* 3(2): 131-132. ISSN: 0264-4754.
NAL Call Number: QL55.I5
Descriptors: body weight, dog feeding, experiments, feeding behavior, food intake, growth rate, social interaction, toxicology, unrestricted feeding, dogs.

Wilson, L.D. and C. Shelat (2003). **Electrophysiologic and hemodynamic effects of sodium bicarbonate in a canine model of severe cocaine intoxication.** *Journal of Toxicology Clinical Toxicology* 41(6): 777-788. ISSN: 0731-3810.
NAL Call Number: RA1190.C5
Abstract: Objective. Cocaine toxicity causes myocardial depression, malignant dysrhythmias, and sudden death, partially due to cocaine-related myocardial sodium channel blockade. Because of cocaine's ability to block cardiac sodium channels, sodium bicarbonate (NaHCO3) has been proposed as an antidote. The hypothesis of this study was that NaHCO3 would correct cocaine-induced conduction abnormalities and resultant hemodynamic compromise in an animal model simulating severe cocaine intoxication. Methods. Design: Prospective, controlled, experimental study in which 15 anesthetized dogs were given three successive boluses of cocaine (7 mg/kg) and then randomized to receive NaHCO3, 2 mEq/kg (n = 8) or placebo (n = 7). Measurements: Arterial, left ventricular, and pulmonary artery pressures; cardiac output (CO); electrocardiogram (ECG); blood gases; and serum concentrations of cocaine were measured at baseline, at fixed time intervals after each bolus of cocaine, and then after administration of NaHCO3 or placebo. Statistical significance was determined by analysis of variance (ANOVA) for repeated measures. Results. Seven dogs experienced significant arrhythmias, including VT, pulseless electrical activity, and third-degree atrioventricular block; 2 of these dogs expired prior to receiving NaHCO3 and were excluded. Immediately after administering NaHCO3, QRS duration decreased by 30% ($p < 0.001$), returning to baseline more quickly than in the control group. This effect was associated with a brief 30% decrease in MAP (p = NS). After NaHCO3, CO increased 78% and remained increased for 5 min ($p < 0.007$). One dog converted from complete heart block to sinus rhythm shortly after NaHCO3 administration. Conclusions. NaHCO3 improved ECG changes secondary to cocaine toxicity and improved myocardial function.
Descriptors: cardiovascular system, transport and circulation, pharmacology, toxicology, cardiac dysrhythmia, heart disease, drug therapy, drug induced, heart block, heart disease, cardiac output, hemodynamics.

Urinary System

Carvalho, M., J.P. Lulich, C.A. Osborne, and Y. Nakagawa (2003). **Role of urinary inhibitors of crystallization in uric acid nephrolithiasis: dalmatian dog model.** *Urology* 62(3): 566-570. ISSN: 0090-4295.

NAL Call Number: RC870

Abstract: Objectives. To study the role of urinary inhibitors on crystallization-nephrocalcin, Tamm-Horsfall protein (THP), and glycosaminoglycans (GAGs)-in hyperuricosuric nephrolithiasis using Dalmatian dogs, a breed well-known for high levels of uric acid excretion, in an in vivo model. Methods. Urine samples were collected from 10 stone-forming Dalmatian dogs and from 5 age-matched Dalmatians without kidney stones. Purine derivatives present in urine were studied by high-performance liquid chromatography. THP, GAGs, and nephrocalcin were isolated and measured. Results. As expected, the Dalmatians excreted a large amount of uric acid in urine, but without differences between the two groups (0.42 +- 0.08 mg/mg creatinine versus 0.48 +- 0.11 mg/mg creatinine for stone-forming and healthy Dalmatians, respectively, P = 0.64). No other metabolites were derived from purine in their urine. Stone-forming Dalmatians showed significantly lower urinary excretion of THP than did normal Dalmatians (0.09 +- 0.03 mg/mg creatinine versus 0.21 +- 0.03 mg/mg creatinine, P <0.03). The urinary excretion of GAGs was lower in the stone-forming Dalmatians, although the difference was not statistically significant. Inhibition of calcium oxalate monohydrate crystal growth caused by nephrocalcin isoforms from healthy and stone-forming dogs were in the same order of apprx10-7 M, as calculated from a Langmuir isotherm type plot. Conclusions. The urinary excretion of THP and GAGs was decreased in stone-forming Dalmatians compared with healthy ones. Our results support the suitability of Dalmatian dogs as an in vivo model to investigate the interrelationship of urine inhibitors of crystallization and hyperuricosuria.

Descriptors: biochemistry and molecular biophysics, metabolism, urinary system, chemical coordination and homeostasis, nephrolithiasis, kidney calculi, urologic disease, high performance liquid chromatography, chromatographic techniques, laboratory techniques, crystallization .

Chen, D., B. Jefferson, S.J. Harvey, K. Zheng, C.J. Gartley, R.M. Jacobs, and P.S. Thorner (2003). **Cyclosporine a slows the progressive renal disease of alport syndrome (x-linked hereditary nephritis): results from a canine model.** *Journal of the American Society of Nephrology* 14(3): 690-698. ISSN: 1046-6673.

Abstract: Alport syndrome refers to a hereditary disorder characterized by progressive renal disease and a multilaminar appearance to the glomerular basement membrane (GBM). In a small group of patients with Alport syndrome, cyclosporine A was reported to decrease proteinuria and maintain stable renal function over 7 to 10 yr of follow-up. The present study examined the effect of cyclosporine A on GBM structure and the progression to renal failure in a canine model of X-linked Alport syndrome. Affected male dogs and normal male dogs treated with cyclosporine A underwent serial renal biopsies. Body weight, serum concentra-

tions of creatinine and albumin, and GFR were sequentially determined. Controls consisted of untreated dogs that developed end-stage renal failure by 8 mo of age. Renal biopsies were assessed for glomerulosclerosis and the percent of multilaminar GBM as measured by image analysis. Significant differences were found between treated and untreated affected dogs for weight, serum creatinine, and GFR. There was a significant delay in the progression of multilaminar change to the GBM, although treated affected dogs at termination had attained approximately 100% split GBM as did untreated affected dogs. A significant difference in the number of sclerotic glomeruli was also noted; treated dogs rarely developed obsolete glomeruli during the period studied. Interstitial fibrosis was not significantly affected by cyclosporine A treatment. These findings indicate that cyclosporine A is beneficial in slowing, but not stopping, the clinical and pathologic progression of Alport syndrome. At least part of this beneficial effect comes from a delayed deterioration of GBM structure, which in turn may be related to glomerular hemodynamics altered by cyclosporine A.
Descriptors: genetics, pharmacology, urinary system, chemical coordination and homeostasis, Alport syndrome, X linked hereditary nephritis, congenital disease, genetic disease, urologic disease, glomerulosclerosis, interstitial fibrosis, disease miscellaneous, renal disease, drug therapy, renal failure, image analysis, imaging and microscopy techniques, laboratory techniques, renal biopsy, glomerular filtration rate, body weight, glomerular hemodynamics.

Choi, E.W. and C.W. Lee (2004). **Development of canine nephrotic syndrome model.** *Journal of Veterinary Medical Science* 66(2): 169-174. ISSN: 0916-7250.
NAL Call Number: SF604.J342
Abstract: To develop an experimental animal model for immune-mediated glomerulonephritis and nephrotic syndrome, nine healthy dogs were sensitized by intravenous injection with 1 mug of endotoxin and 5 mg of native bovine serum albumin. After 1 week, 120 mg of cationized bovine serum albumin was injected intravenously 5 times a week. Among nine dogs, five dogs were confirmed as having developed glomerulonephritis and nephrotic syndrome by increase of urine protein-to-creatinine ratio (>1.0), hypoalbuminemia (<1.5 g/dl), hypercholesterolemia (>240 mg/dl), and edema. This model should be useful for studying immune-mediated glomerulonephritis and nephrotic syndrome.
Descriptors: immune system, chemical coordination and homeostasis, urinary system, veterinary medicine, medical sciences, glomerulonephritis, immune system disease, urologic disease, nephrotic syndrome, animal model development, urinary protein to creatinine ratio.

Fryer, R.M., L. Preusser, S. Calzadilla, Y. Hu, H. Xu, K. Marsh, B. Cox, C.T. Lin, M. Gopalakrishnan, and G. Reinhart (2004). **A-278637, a novel atp-sensitive potassium channel opener: hemodynamic comparison to zd-6169, way-133537 and nifedipine in the anesthetized canine**. *FASEB Journal* 18(4-5): Abst. 404.3. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: cardiovascular system, transport and circulation, pharmacology, urinary system, chemical coordination and homeostasis, overactive bladder, urinary incontinence, urologic disease, therapy .

Halpenny, M., F. Markos, H.M. Snow, P.F. Duggan, E. Gaffney, D.P. O'Connell, and G.D. Shorten (2001). **Effects of prophylactic fenoldopam infusion on renal blood flow and renal tubular function during acute hypovolemia in anesthetized dogs.** *Critical Care Medicine.* 29(4): 855-860. ISSN: 0090-3493.

Abstract: OBJECTIVE: It was hypothesized that fenoldopam mesylate, a selective dopamine agonist, may preserve renal perfusion and decrease tubular oxygen consumption during states of hypoperfusion, such as hypovolemic shock. The objective of this study was to quantify the effects of fenoldopam (0.1 microg x kg(-1) x min(-1)) on renal blood flow, urine output, creatinine clearance, and sodium clearance in pentobarbital anesthetized dogs that had undergone partial exsanguination to acutely decrease cardiac output. DESIGN: Prospective, randomized, controlled experiment. SETTING: University-based animal laboratory and research unit. SUBJECTS: Eight female beagle dogs. INTERVENTIONS: Arterial blood pressure, heart rate, cardiac output, renal blood flow, urine output, creatinine clearance, and fractional excretion of sodium were measured and calculated at four times: a) before infusion of fenoldopam or normal saline; b) during infusion of fenoldopam or normal saline (1 hr); c) during a 90-min period of hypovolemia (induced by acute partial exsanguination), with concurrent infusion of fenoldopam or normal saline; and d) during a 1-hr period after retransfusing the dogs. MEASUREMENTS AND MAIN RESULTS: Administration of fenoldopam (0.1 microg x kg(-1) x min(-1)) was not associated with hemodynamic instability. Renal blood flow and urine output decreased significantly from baseline (p <.01) during the hypovolemic period in the placebo group (72 +/- 20 to 47 +/- 6 mL/min and 0.26 +/- 0.15 to 0.08 +/- 0.05 mL/min, respectively) but not in the fenoldopam group (75 +/- 14 to 73 +/- 17 mL/min and 0.3 +/- 0.19 to 0.14 +/- 0.05 mL/min, respectively). Creatinine clearance and fractional excretion of sodium decreased significantly from baseline (p <.01) in the placebo group during the hypovolemic period (3.0 +/- 0.4 to 1.8 +/- 0.8 mL x kg(-1) x min(-1) and 1.7% +/- 0.9% to 0.4% +/- 0.2%, respectively) but not in the dogs that received fenoldopam (3.0 +/- 1.0 to 2.9 +/- 0.5 mL x kg(-1) x min(-1) and 1.9% +/- 1.1% to 1.7% +/- 2.7%, respectively). CONCLUSIONS: Fenoldopam ablated the tubular prerenal response to profound hypovolemia and maintained renal blood flow, glomerular filtration rate, and natriuresis without causing hypotension. This suggests that fenoldopam may have a renoprotective effect in acute ischemic injury.

Descriptors: animal model, female, beagle dogs, hypovolemia, fenoldopam, blood flow, glomerular filtration rate, natriuresis.

Hoag, J.B., M. Liu, R.B. Easley, M.F. Britos Bray, P. Kesari, H. Hassoun, M. Haas, R.M. Tuder, H. Rabb, and B.A. Simon (2008). **Effects of acid aspiration-induced acute lung injury on kidney function.** *American Journal of Physiology. Renal Physiology* 294(4): F900-8. ISSN: 0363-6127.

Abstract: Acute lung injury (ALI) in combination with acute kidney injury carries a mortality approaching 80% in the intensive care unit. Recently, attention has focused on the interaction of the lung and kidney in the setting of ALI and mechanical ventilation (MV). Small animal models of ALI and MV have demonstrated changes in inflammatory mediators, water channels, apoptosis, and function in the kidney early in the course of injury. The purpose of this investigation was to test the hypothesis that ALI and injurious MV cause

early, measurable changes in kidney structure and function in a canine HCl aspiration model of ALI when hemodynamics and arterial blood gas tensions are carefully controlled. Intratracheal HCl induced profound ALI as demonstrated by increased shunt fraction and airway pressures compared with sham injury. Sham-injured animals had similar mean arterial pressure and arterial Pco(2) and HCO(3) levels compared with injured animals. Measurements of renal function including renal blood flow, urine flow, serum creatinine, glomerular filtration rate, urine albumin-to-creatinine ratio, and kidney histology scores were not different between groups. With maintenance of hemodynamic parameters and alveolar ventilation, ALI and injurious MV do not alter kidney structure and function early in the course of injury in this acid aspiration canine model. Kidney injury in large animal models may be more similar to humans and may differ from results seen in small animal models.
Descriptors: hydrochloric acid toxicity, kidney function tests, lung diseases etiology, lung injury, administration, inhalation, blood pressure drug effects, carbon dioxide blood, cardiac output drug effects, creatinine blood, diuresis drug effects, dogs, glomerular filtration rate drug effects, hydrochloric acid administration and dosage, hydrogen ion concentration, lung drug effects, lung pathology, models, animal, pulmonary alveoli drug effects, pulmonary alveoli pathology.

Janssens, L.A.A. and S. Peeters (1997). **Comparisons between stress incontinence in women and sphincter mechanisms incompetence in the female dog**. *Veterinary Record* 141(24): 620-625. ISSN: 0042-4900.
NAL Call Number: 41.8 V641
Descriptors: comparisons, women, urinary incontinence, sphincters, bladder, urethra, stresses, physiopathology, treatment.

Kaewsakhorn, T., M. Gower, W. Kisseberth, C. Capen, M. Calverley, and N. Inpanbutr (2004). **Effects of calcitriol and medium chain triglyceride (mct) on cell growth of the canine transitional cell carcinoma of the urinary bladder (tcc) in vitro**. *FASEB Journal* 18(4-5): Abst. 68.8. ISSN: 0892-6638.
NAL Call Number: QH301.F3
Descriptors: calcitriol , cell biology, cell proliferation, pharmacology, tumor biology, bladder transitional cell carcinoma, neoplastic disease, urologic disease, therapy, western blot, genetic techniques, laboratory techniques, drug regimen.

Konety, B.-R., T.-S. Griffith, S.-J. Sirintrapun, J.-M. Rippentrop, A.-H. Stolpen, B.-R. De-Young, T.-L. Ratliff, and R.-D. Williams (2003). **Effect of intra-prostatic injection of adenovirus-trail in vivo in the dog prostate.** *Journal of Urology* 169(4 Supplement): 212. ISSN: 0022-5347.
NAL Call Number: 448.8 J8234
Descriptors: methods and techniques, molecular genetics, biochemistry and molecular biophysics, reproductive system, reproduction , h and e staining, hematoxylin eosin staining, histology and cytology techniques, laboratory techniques, intra prostatic injection, clinical techniques, pelvic computed tomography, imaging and microscopy techniques, radical prostatectomy, therapeutic and prophylactic techniques, periprostatic inflammation.

Marcovich, R., A.L. Williams, B.D. Seifman, and J.S.J. Wolf (2000). **Development of a canine model to assess the biochemical stress response to laparoscopic and open surgery**. *Journal of Endourology* 14(Supplement 1): A3. ISSN: 0892-7790.
Descriptors: urinary system, chemical coordination and homeostasis, methods and techniques, pneumoperitoneum, laparoscopic nephrectomy, open nephrectomy, biochemical stress response, surgical stress response, meeting abstract

Nanri, M., N. Mori, T. Kirimoto, T. Uji, and M. Kiniwa (2004). **The effect of propiverine hydrochloride in a canine urinary frequency model associated with bladder hyperactivity.** *Journal of Pharmacological Sciences* 94(Supplement 1): 265P. ISSN: 1347-8613.
Descriptors: pharmacology, urinary system, chemical coordination and homeostasis, veterinary medicine, medical sciences, bladder hyperactivity, urologic disease, lower urinary tract dysfunction, urologic disease, micturition interval

Olson, M.E. and R. Hjelm (2008). **Canine bladder tissue responses to injectable stabilized non-animal hyaluronic acid/dextranomer (NASHA/Dx) gel.** *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 138(1): 114-5. ISSN: 0301-2115.
Descriptors: biocompatible materials administration and dosage, dextrans administration and dosage, foreign body migration pathology, foreign body reaction pathology, hyaluronic acid administration and dosage, urinary bladder drug effects, dogs, foreign bodies, gels, injections, microspheres, models, animal, urinary incontinence, stress drug therapy.

Pomeroy, M.J. and J.L. Robertson (2004). **The relationship of age, sex, and glomerular location to the development of spontaneous lesions in the canine kidney: analysis of a life-span study**. *Toxicologic Pathology* 32(2): 237-242. ISSN: 0192-6233.
Abstract: It is well documented that the presence of spontaneous renal disease and renal dysfunction increases with age in many species of mammals. Such alterations in renal structure and function may significantly affect the interpretation of long-term toxicology studies. The purpose of the present study was to assess the temporal evolution of selected renal lesions (cysts, interstitial inflammation, interstitial fibrosis, and glomerulosclerosis) in laboratory Beagle dogs, an important animal model in chronic toxicology studies. We examined representative sections of the kidneys from 159 purpose-bred and laboratory housed Beagle dogs and analyzed the extent and distribution of spontaneous lesions using the World Health Organization classification system for renal lesions. All dogs examined had renal lesions of varying severities. In the youngest dogs (up to 2 years of age), the density and severity of lesions were minimal, but were more severe by middle age (defined as 3-7 years). The density and severity of interstitial fibrosis and inflammation progressed with advancing age ($p<0.0001$ for both) in both sexes. The density of tubular cysts increased linearly with advancing age in females ($p=0.0006$), but not in males ($p=0.49$). The cortical distribution of glomeruli and advancing age of dogs were significantly related to the development of glomerulosclerosis. As age increased, the presence of glomerulosclerosis increased ($p=0.0008$). These data indicate that the development of renal lesions is progressive over the lifetime of a genetically similar population of laboratory Beagle dogs maintained under optimal standard environmental conditions. This information may be useful in the interpretation of compound effects during chronic toxicology studies in the dog.

Descriptors: breed, Beagle, age differences, aging, cysts pathological, fibrosis, glomerulus, inflammation, kidney diseases, lifespan, sex differences.

Salomon, C., D. Casanova, G. Solares, C. Qualls, J. Gonzalez Cotorruelo, and M. Arias (2007). **Blood volume expansion with hyperoncotic colloids deteriorates allograft function in a canine model of renal transplantation.** *Transplantation Proceedings* 39(7): 2112-4. ISSN: 0041-1345.

NAL Call Number: RD120.7.T68

Abstract: PURPOSE: We investigated the effects of acute maximal hydratation with hemoce (H) and dextran-40 (D40) on the postoperative graft function, following renal transplantation (RT) in a canine model. METHODS: After induction of anesthesia with pentobarbital (5 mg/kg), 18 beagle dogs were randomized to receive either saline solution to increase the central venous pressure (CVP) to 5 mm Hg (GI); H solution to increase the CVP to 10 mm Hg (GII); or D40 to achieve 15 mm Hg (GIII), before reperfusion. A pulmonary artery catheter was used to measure CVP, mean pulmonary artery pressure, and cardiac output (CO). The surgical procedure consisted of autotransplantation of the dog's left kidney an hour prior to cold ischemia with University of Wisconsin solution, followed by contralateral nephrectomy. Diuresis, creatinine (Cr), and BUN levels were measure at 24 hours before RT, as well as 24, 48, and 72 hours after the procedure. RESULTS: Only in the treated groups did cardiac filling pressures and CO increase as a result of hydration. Only in the GI group did serum Cr and blood urea nitrogen significantly peak at the second postoperative day while it continued to increase at two (GII) and three (GIII) times greater than GI on the third day. Histological examination showed osmotic nephrosis like-lesions only among treated grafts. CONCLUSION: We concluded that maximal hydration with H and D40 colloid deteriorated postoperative graft function after RT. We believe that in the future the effects of any colloid solution should be tested in an animal model in the fashion as we have described, in order to know which one, and at what dose, is the safest to improve kidney allograft outcome.

Descriptors: blood volume physiology, colloids therapeutic use, kidney transplantation physiology, transplantation, homologous physiology, blood pressure, blood urea nitrogen, creatinine blood, dogs, models, animal.

Shau, Y.W., S.H. Pao, N.K. Chou, K.J. Chang, and J.J. Shyu (2009). **Renal vascular perfusion index in a canine model.** *Ultrasound in Medicine and Biology* 35(1): 36-43.

NAL Call Number: QC244.U4

Abstract: Decreased renal perfusion plays an important role in the progression toward renal failure. In this study, a novel measure was proposed to quantify renal perfusion using canine model. Serial renal vascular images at different vascular areas including the whole vascular tree, interlobar, arcuate and interlobular vessels were captured. Image processing software was designed to analyze the changes of power Doppler intensity of colored pixels within regions-of-interest (ROI). For a given ROI, the power Doppler vascular index (PDVI) was found to fluctuate with the cardiac cycle. It was also noted that the power Doppler signals generated by arterial vessels have different fluctuating waveforms and different phase compared with the signal derived from venous vessels. A power Doppler correlation-map was developed to differentiate the arteries and veins in the ROI. Using the serial power Doppler images and the

derived flow direction information, the interlobular perfusion can be strongly quantified. The renal vascular perfusion index (RVPI) defined as the ratio of PDVI(max) versus PDVI(min) was significantly higher in the interlobular vessel areas than three other areas for seven healthy dogs. The RVPI resembles the systolic/diastolic (S/D) ratio that commonly reflects arterial hemodynamics. RVPI and power Doppler correlation-map reveal more "dynamic" sense of vascular perfusion and provide a novel approach for the examination of renal function in clinical practice.

Descriptors: image processing, computer assisted, kidney ultrasonography, renal circulation physiology, ultrasonography, doppler, color methods, blood flow velocity, dogs, kidney function tests, models, animal, perfusion, renal artery ultrasonography, renal veins ultrasonography.

Tomiyama, Y., M. Murakami, Y. Yamazaki, M. Kojima, and M. Akahane (2003). **Comparison between cl-316243- and cgp-12177a-induced relaxations in isolated canine ureter.** *Pharmacology* 68(3): 140-146. ISSN: 0031-7012.

NAL Call Number: RM1.P473

Abstract: We compared the effects of CL-316243, a selective beta3-adrenoceptor agonist, and CGP-12177A, a nonconventional partial beta-adrenoceptor agonist, on the KCl-induced contraction in the isolated canine ureter. CL-316243 concentration dependently relaxed the ureteral contraction, the pD2 value being 7.75 +- 0.11. This relaxation was competitively antagonized by the selective beta3-adrenoceptor antagonist SR58894A and by the nonselective beta-adrenoceptor antagonist bupranolol, their pA2 values being 7.08 +- 0.08 and 6.43 +- 0.09, respectively. CGP-12177A concentration dependently reduced the KCl-induced contraction, the pD2 value being 6.30 +- 0.25. Even at 1 X 10-5 mol/l, CGP-20712A (a selective beta1-adrenoceptor antagonist) did not shift the concentration-response curves for CL-316243 or CGP-12177A. SR58894A did not induce a parallel rightward shift in the concentration-response curve for CGP-12177A, but bupranolol did produce such a shift, pA2 and slope values in the Schild plot being 7.15 +- 0.77 and 0.60 +- 0.15, respectively. Hence, the competition characteristics for SR58894A and bupranolol differed between the CL-316243-induced and CGP-12177A-induced relaxations. Our results suggest that CGP-12177A produces ureteral relaxation in the dog via an atypical beta-adrenoceptor (possibly, an atypical site/state of the beta3-adrenoceptor) as well as via the typical beta3-adrenoceptor.

Descriptors: biochemistry and molecular biophysics, pharmacology, urinary system, chemical coordination and homeostasis, concentration response curves.

Wuensch, S., M. Gekle, U. Kersting, B. Schuricht, and H. Oberleithner (1995). **Phenotypically and karyotypically distinct madin-darby canine kidney cell clones respond differently to alkaline stress**. *Journal of Cellular Physiology* 164(1): 164-171. ISSN: 0021-9541.

NAL Call Number: 444.8 J822

Abstract: We isolated two cell clones from the wild-type Madin-Darby canine kidney cell line (MDCK) that resembles renal collecting duct epithelium. Morphology and karyotypes of the two cell clones were evaluated. The MDCK-C7 cell clone morphologically resembles principal cells (polygonal cell shape, flat), while the MDCK-C11 clone resembles intercalated cells (cuboidal cell shape, high). The diploid chromosome number of MDCK-C7 cells is 83.1 +- 0.2 (n = 139); that for MDCK-C11 cells is 78.8 +- 0.1 (n = 128). Culture

of MDCK-C7 cells in alkaline medium (pH 7.7) induced irreversible phenotypical and genotypical alterations. Transformed MDCK-C7F cells are characterized by two abnormal (biarmed) chromosomes. In contrast, MDCK-C11 cells are not phenotypically altered by alkaline stress. In order to elucidate the role of intracellular pH (pH-i) in the transformation process, we measured pH-i under control conditions (pH 7.4), after 5 min exposure to alkaline stress ("acute experiment," pH 7.7) and after incubation of the cells in alkaline medium for two weeks ("chronic experiment," pH 7.7). Under control conditions, MDCK-C7 cells maintained pH, at 7.14 +- 0.01 (n = 154) and MDCK-C11 cells at 7.01 +- 0.01 (n = 147). Acute alkaline stress increased pH-i of both cell types to similar steady-state values. Under chronic alkaline stress, MDCK-C7 cells were unable to maintain intracellular pH within normal limits exhibiting sustained alkalinization, whereas MDCK-C11 cells could successfully regulate pH-i. We conclude that wild-type MDCK cells consist of two genetically distinct subpopulations with different morphology and function. Only the MDCK-C7 clone that resembles the principle cell type of renal collecting duct can be transformed by alkaline stress while the MDCK-C11 clone resists this treatment, due to efficient pH-i control mechanisms.
Descriptors: cell biology, development, genetics, morphology, urinary system, chemical coordination and homeostasis, alkalinization, ph, proliferation, ultrastructure .

Wynn, V.M., E.B. Davidson, R.G. Higbee, J.W. Ritchey, T.D. Ridgway, K.E. Bartels, and M.D. Lucroy (2003). **In vitro effects of pulsed holmium laser energy on canine uroliths and porcine cadaveric urethra.** *Lasers in Surgery and Medicine* 33(4): 243-6. ISSN: 0196-8092.
Descriptors: animal model, human lithotripsy procedures, holmium laser energy, canine uroliths, porcine urethra.