

Henry Ford Health System Publication List March 2006

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You can access this page at http://www.henryford.com/body_nologin.cfm?id=46638.

Ardanaz, N. and P. J. Pagano (2006). "Hydrogen peroxide as a paracrine vascular mediator: regulation and signaling leading to dysfunction." *Exp Biol Med (Maywood)* **231**(3): 237-51.

[PDF Full-Text](#)

Numerous studies have demonstrated the ability of a variety of vascular cells, including endothelial cells, smooth muscle cells, and fibroblasts, to produce reactive oxygen species (ROS). Until recently, major emphasis was placed on the production of superoxide anion (O₂(⁻)) in the vasculature as a result of its ability to directly attenuate the biological activity of endothelium-derived nitric oxide (NO). The short half-life and radius of diffusion of O₂(⁻) drastically limit the role of this ROS as an important paracrine hormone in vascular biology. On the contrary, in recent years, the O₂(⁻) metabolite hydrogen peroxide (H₂O₂) has increasingly been viewed as an important cellular signaling agent in its own right, capable of modulating both contractile and growth-promoting pathways with more far-reaching effects. In this review, we will assess the vascular production of H₂O₂, its regulation by endogenous scavenger systems, and its ability to activate a variety of vascular signaling pathways, thereby leading to vascular contraction and growth. This discussion will include the ability of H₂O₂ to (i) initiate calcium flux as well as (ii) stimulate pathways leading to sensitization of contractile elements to calcium. The latter involves a variety of protein kinases that have also been strongly implicated in vascular hypertrophy. Previous intensive study has emphasized the ability of NADPH oxidase-derived O₂(⁻) and H₂O₂ to activate these pathways in cultured smooth muscle cells. However, growing evidence indicates a considerably more complex array of unique oxidase systems in the endothelium, media, and adventitia that appear to participate in these deleterious effects in a sequential and temporal manner. Taken together, these findings seem consistent with a paracrine effect of H₂O₂ across the vascular wall.

Attallah, N., L. Yassine, et al. (2005). "Risk of bleeding and restenosis among chronic kidney disease patients undergoing percutaneous coronary intervention." *Clin Nephrol* **64**(6): 412-8.

[PDF Full-Text \(User name=hfhs / Password=t424616w\)](#)

BACKGROUND: Bleeding risk is increased in renal failure due to impaired platelet adhesiveness. Patients who undergo percutaneous coronary intervention (PCI) are given multiple antiplatelet agents that increase that risk. We retrospectively tested the hypothesis that chronic kidney disease (CKD) patients who undergo PCI are at higher risk of bleeding and restenosis (due to chronic inflammation) compared to patients with normal renal function. **METHODS:** Patients who had PCI for non-ST elevation myocardial infarction or unstable angina between July 2001 and June 2003 (1,184 patients) were included in the study. All the patients were given periprocedural clopidogrel, aspirin and glycoprotein IIb/IIIa inhibitor if indicated, and then continued on clopidogrel and aspirin daily for 12 months. The patients were classified into 5 groups according to the CKD stage and followed-up for 12 months for development of major or minor bleeding, restenosis, length of hospital stay and survival. **RESULTS:** The incidence

of major bleeding within the first month (3.4% in normal kidney function patients (Gp 1), 4.8% for CKD Stages 1 and 2 patients (Gp2), 5.2% for CKD Stage 3 patients (Gp3), 6.1% for CKD Stage 4 patients (Gp4) and 9.3% for CKD Stage 5 patients (Gp5), $p = 0.001$) and for minor bleeding (5.7% in Gp1, 6.5% for Gp2, 7.4% for Gp3, 9.2% for Gp4 and 11.3% for Gp5, $p = 0.001$) and the incidence of restenosis at one month (4.6% in Gp1, 5.3% for Gp2, 6.8% for Gp3, 7.3% for Gp4 and 9.6% for Gp5, $p = 0.001$) and 6 months (11.2% in Gp1, 13.5% for Gp2, 15.7% for Gp3, 16.4% for Gp4 and 19.7% for Gp5, $p = 0.001$) were higher with worsening CKD. Survival at one year was worse with worsening of the kidney function. **CONCLUSION:** Worsening of CKD is associated with progressively increased risk of minor and major bleeding, restenosis and death during and after PCI.

Badani, K. K., A. Bhandari, et al. (2005). "Comparison of two-dimensional and three-dimensional suturing: is there a difference in a robotic surgery setting?" *J Endourol* **19**(10): 1212-5. [PDF Full-Text](#)

BACKGROUND AND PURPOSE: Robotic surgery allows three-dimensional (3D) viewing of tissues. We compared two-dimensional (2D) and 3D suturing drills using the daVinci surgical system to determine if the latter is advantageous. **MATERIALS AND METHODS:** Twenty-eight anastomotic drills were completed by seven surgeons using the daVinci robot. Three surgeons had considerable (>6 months) robotic experience, and four had none. Drills were performed randomly in both dimensional modes in a blinded fashion. Drill 1 was an interrupted four stitch and drill 2 a running closure. All tasks were kept uniform. We recorded time to completion, difficulty, and accuracy. The drills were evaluated by two independent reviewers for accuracy and major errors (i.e., broken suture, torn graft). **RESULTS:** The average operative time per drill in two dimensions was 13.1 minutes (range 6.9-21.9 minutes) and in three dimensions was 8.5 minutes (range 4.7-12.8 minutes) ($P < 0.001$). Drill 1 was 6.1 minutes faster in three dimensions (mean 9.2 minutes; $P < 0.01$), and drill 2 was 2.9 minutes faster (mean 7.8 minutes; $P = 0.03$). Both advanced and novice groups were faster in 3D ($P < 0.01$). There were two major errors in the 3D performances and 5 in the 2D exercises ($P < 0.05$). The participants correctly identified the dimensional mode 92.9% of the time ($P < 0.01$). **CONCLUSION:** The anastomosis was completed 65% faster using 3D with equal, if not greater, accuracy. Drill 1 was improved to a greater degree than drill 2, suggesting most benefit of 3D views during knot tying. Use of three dimensions outperformed two dimensions in both groups. Surgeons can immediately benefit from 3D viewing during robotic surgery.

Besarab, A. and S. Soman (2005). "Anemia management in chronic heart failure: lessons learnt from chronic kidney disease." *Kidney Blood Press Res* **28**(5-6): 363-71. **Full-Text Not Available / [Click for Article Request Form](#)**

The importance of anemia in chronic kidney disease (CKD) has become increasingly well recognized over recent years, as have the benefits of treating anemic CKD patients with recombinant human erythropoietin (rHuEPO, epoetin). As well as reducing the need for blood transfusions and the complications associated with renal failure in CKD patients, rHuEPO treatment decreases patient morbidity and mortality, particularly as a result of cardiovascular disease. The strong correlation between anemia, renal failure and cardiac failure is one that has received much attention recently, with each factor recognized to cause the other to worsen in a 'vicious cycle'. Recent studies have concentrated on the possible benefits of anemia treatment in patients with CHF. Currently available data suggest improvements in CHF symptoms, left ventricular ejection fraction (LVEF) and a reduction of hospitalizations associated with anemia correction through epoetin treatment. Available data from CKD patients suggest that anemia management should begin as early as possible, although the optimal target level for individual patients is as yet unclear. In addition to the currently available evidence, additional large, randomized, controlled studies are required to further define the morbidity/mortality benefits of epoetin treatment in CHF patients with anemia.

Coffey, C. Edward, Editor. Pediatric neuropsychiatry. Philadelphia: Lippincott Williams & Wilkins, 2006. **Sladen Call Number WS 340 P371345 2006**

Deeb, D. D., H. Jiang, et al. (2005). "Chemosensitization of hormone-refractory prostate cancer cells by curcumin to TRAIL-induced apoptosis." *J Exp Ther Oncol* **5**(2): 81-91. **Full-Text Not Available / [Click for Article Request Form](#)**

Failure to undergo apoptosis has been implicated in the resistance of tumor cells to anticancer therapies. Promotion of apoptosis in tumor cells could potentially increase the efficacy of conventional treatment regimens and improve prognosis. Prostate cancer cells are generally resistant to induction of apoptosis by anticancer agents and death ligands. We investigated the sensitization of prostate cancer cell lines by curcumin (diferuloyl-methane) to TNF-related apoptosis inducing ligand (TRAIL)-induced apoptosis. Prostate cancer cells treated with curcumin or TRAIL or curcumin and TRAIL together were assessed for induction of apoptosis and pathway of apoptosis was determined from the activation of procaspases and release of cytochrome c from mitochondria. Curcumin sensitized LNCaP, DU145 and PC3 tumor cell lines to TRAIL. Combined curcumin and TRAIL treatment produced the most loss of viable cells by inducing apoptosis as revealed by accumulation of hypodiploid cells in sub-G1 phase, enhanced annexin V binding, DNA fragmentation, cleavage of procaspases-3, -8, and 9, truncation of proapoptotic Bid, and release of cytochrome c from mitochondria. Tumor cells expressed constitutively active NF-kappaB and sensitization to TRAIL involved inhibition of NF-kappaB by curcumin. These findings suggest that combined curcumin/TRAIL chemo-immunotherapy may be a beneficial adjunct to the standard therapeutic regimens for prostate cancer.

Gao, X., D. Deeb, et al. (2005). "Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome c from mitochondria." *J Exp Ther Oncol* **5**(1): 39-48. **Full-Text Not Available** / [Click for Article Request Form](#)

Malignant glioma cells are generally resistant or only weakly sensitive to tumor necrosis factor family of cell death-inducing ligands, including TNF-related apoptosis-inducing ligand (TRAIL)/Apo2L. The chemopreventive activity of polyphenolic compounds present in plant-derived food products has been well recognized in epidemiological studies; however, the mechanism of chemoprevention by these dietary constituents largely remains unknown. Curcumin, the yellow pigment in the spice turmeric, has profound anti-inflammatory activity and exhibits chemopreventive and tumor growth inhibitory activity. In the present study, we investigated whether curcumin sensitizes malignant glioma cell lines U251MG and U87MG to TRAIL-induced apoptosis. Treatment with low concentrations (5-20 microM) of curcumin alone had no effect on the viability of either cell line. At low concentration (5 ng/ml) TRAIL induced cytotoxicity in U251MG cells but not in U87MG cells. Whereas curcumin at subtoxic concentration sensitized U87MG cells to TRAIL-induced cytotoxicity, it had no effect on TRAIL-mediated cytotoxicity in U251MG cells. The combined curcumin and TRAIL treatment enhanced accumulation of hypo-diploid U87MG cells in sub G1 cell cycle phase and induced the cleavage of procaspases-3, -8, -9 and release of cytochrome c from mitochondria. These data indicate that curcumin differentially sensitizes glioma cells to TRAIL-induced apoptosis through the activation of both extrinsic (receptor-mediated) and intrinsic (chemical-induced) pathways of apoptosis. These results define a potential use of curcumin to sensitize glioma cells for TRAIL-mediated immunotherapy.

Greenbaum, A. B., C. L. Grines, et al. (2006). "Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial." *Am Heart J* **151**(3): 689 e1-689 e10. [PDF Full-Text](#)

BACKGROUND: Platelet-initiated acute thrombosis and coronary embolization are fundamental in the pathophysiology of complications during percutaneous coronary intervention (PCI). Cangrelor (formerly AR-C69931MX) is a novel, rapidly acting, intravenous, specific antagonist of platelet aggregation via binding to the adenosine diphosphate (ADP) P2Y12 receptor subtype. The primary aims of this study were to assess the initial safety and pharmacodynamics of cangrelor in patients undergoing PCI. **METHODS:** In part 1, patients undergoing PCI were randomized to an 18- to 24-hour of either placebo, 1-, 2-, or 4-microg/kg per minute cangrelor in addition to aspirin and heparin beginning before PCI. In part 2, patients were randomized to receive either cangrelor (4 microg/kg per minute) or abciximab before PCI. The primary end point was the composite incidence of major and minor bleeding through 7 days. Secondary end points included the occurrence of major adverse coronary events (death, MI, and unplanned repeat coronary intervention) through 30 days plus ex vivo platelet aggregation and bleeding times. **RESULTS:** Two hundred patients (3 dosage groups and placebo) were studied in part 1, and 199 additional patients were then randomized in the second part, comparing 1 dose of cangrelor and abciximab. Combined major and minor bleeding occurred in 13% of those receiving cangrelor and in 8% in those randomized to placebo (P = non significant [NS]) during part 1 and in 7% receiving cangrelor compared with 10% randomized to

abciximab (P = NS), during part 2. The 30-day composite incidence of adverse cardiac events was similar between those receiving cangrelor and those receiving abciximab during part 2 (7.6% vs 5.3%, respectively, P = NS). Mean inhibition of ex vivo platelet aggregation in response to 3 micromol/L ADP at steady state was 100% for both cangrelor 4 microg/kg per minute and abciximab groups in part 2. After termination of infusion, platelet aggregation returned to baseline response more rapidly with cangrelor compared with abciximab. There was a trend toward longer bleeding time prolongation and lower platelet count with abciximab compared with cangrelor.

CONCLUSIONS: This initial experience with intravenous cangrelor during PCI suggests an acceptable risk of bleeding and adverse cardiac events while achieving rapid, reversible inhibition of platelet aggregation via competitive binding to the ADP P2Y₁₂ platelet receptor with less prolongation of bleeding time than the glycoprotein IIb/IIIa receptor antagonist abciximab.

Gupta, R. C., S. Mishra, et al. (2005). "Improvement of cardiac sarcoplasmic reticulum calcium cycling in dogs with heart failure following long-term therapy with the Acorn Cardiac Support Device." *Heart Fail Rev* **10**(2): 149-55. **Full-Text Not Available / [Click for Article Request Form](#)**

Abnormal Ca(2⁺)-homeostasis is a hall-marked characteristic of the failing heart. In the normal myocardium, the sarcoplasmic reticulum (SR) is a principal organelle that controls intracellular Ca(2⁺) concentration during the cardiac cycle. The SR consists of longitudinal and terminal cisterna regions. The former contains the Ca(2⁺)-ATPase pump or SERCA-2a whose function is to transport cytosolic Ca(2⁺) into the lumen of the SR during diastole and whose activity is regulated by reversible phosphorylation of the endogenously SR-bound phospholamban (PLB). The SR's terminal cisterna region contains ryanodine-sensitive Ca(2⁺)-release channels (RR), the activity of which is regulated by direct and indirect reversible phosphorylation. These channels release the SR-stored Ca(2⁺) during contraction. We have shown that in left ventricular (LV) myocardium from dogs with coronary microembolization-induced heart failure, ability of the SR to sequester and release Ca(2⁺) during the cardiac cycles is impaired. This abnormality was associated with reduced expression (protein and mRNA) levels of Ca(2⁺)-ATPase, PLB, and reduced PLB phosphorylation. Long-term therapy with the Acorn Cardiac Support Device (CSD) is associated with restoration of the ability of the SR to sequester Ca(2⁺). This improvement in SR function following chronic CSD therapy was due primarily to increased affinity of the SERCA-2a for calcium. The later was associated with (1) increased phosphorylation of PLB at serine 16 and threonine 17, (2) unchanged protein expression of PLB and (3) unchanged protein expression of SERCA-2a in LV myocardium of CSD-treated dogs compared to controls. This review summarizes our current understanding of the role of the CSD in modulating SR calcium cycling in an experimental canine model of chronic heart failure produced by multiple sequential intracoronary microembolizations.

Kaul, S., N. L. Shah, et al. (2006). "Learning curve using robotic surgery." *Curr Urol Rep* **7**(2): 125-9. **Full-Text Not Available / [Click for Article Request Form](#)**

The da Vinci (Intuitive Surgical, Inc., Sunnyvale, CA) surgical system is being used by an increasing number of surgeons across several surgical specialties. The robotic interface is different not only to open surgery, but also to laparoscopy because it involves remote surgical control, stereoscopic vision, and lack of haptic feedback. As the transition is made from traditional open to robotic surgery, factors such as learning of robotic skills, assessment of proficiency in robotics, and structured training for urologists in practice and residents assumes importance. Understanding how the robotic surgical technique is learned and how such learning can be best assessed will enable us to define protocols for training and set standards for proficiency. Learning curve and surgical dexterity are two parameters that are used to compare surgical learning and training. This article presents the current gold standard for assessing skill training and compares surgical skill acquisition and proficiency using conventional laparoscopy and robotic interfaces.

Kim, D. Y., D. S. Kwon, et al. (2006). "Successful Embolization of Hepatocellular Carcinoma With Yttrium-90 Glass Microspheres Prior to Liver Transplantation." *J Gastrointest Surg* **10**(3): 413-416. **Full-Text Not Available / [Click for Article Request Form](#)**

We report a case of a patient with end-stage liver disease secondary to hepatitis C, complicated by a large hepatocellular carcinoma. Because of the size of the tumor exceeded the Milan criteria, he was not a candidate for liver transplantation. However, after two treatments with yttrium-90 glass microsphere infusions, the tumor became

smaller and the patient's alpha-fetoprotein level dropped to normal range. He was listed for transplantation and subsequently received a deceased donor liver transplant. Two years after his transplantation, he remains tumor free and has normal alpha-fetoprotein levels. This is the first reported case in the literature of using yttrium-90 microspheres as a bridge to liver transplantation in a patient with a large hepatocellular carcinoma. This therapy should be considered in patients with cirrhosis and large hepatocellular carcinomas exceeding current size criterion, who would otherwise be good candidates for transplantation.

Kruger, D. F., C. L. Martin, et al. (2006). "New insights into glucose regulation." Diabetes Educ **32**(2): 221-8. **Full-Text Not Available / [Click for Article Request Form](#)**

This review article describes the regulation of glucose homeostasis in subjects with and without diabetes based on the emergence of new information and discusses modes of action, attributes, and limitations of current diabetes therapies. In normal physiology, glucose homeostasis is tightly controlled by the interaction of pancreatic and gut hormones. Since the 1920s, diabetes has been viewed as a disease caused by deficient secretion of insulin, resulting in reduced glucose uptake and subsequent hyperglycemia. The discovery in the 1950s of the pancreatic hormone glucagon, which opposes insulin by increasing glucose appearance in the circulation, resulted in a bihormonal model of glucose homeostasis. More recently, with the discovery of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) in the 1970s and the pancreatic hormone amylin in the 1980s, it is now understood that several organs and hormones play roles in maintaining glucose homeostasis. Therapies for diabetes have focused on compensation for deficient insulin action through stimulation of insulin secretion, administration of insulin itself, reduction of peripheral insulin resistance, or decreased glucose absorption from the intestine. The discoveries of amylin and GLP-1 have furthered our understanding of the abnormalities involved in diabetes, enabling the development of additional therapeutic options.

Li, L., Q. Jiang, et al. (2006). "Ischemic cerebral tissue response to subventricular zone cell transplantation measured by iterative self-organizing data analysis technique algorithm." J Cereb Blood Flow Metab. **Full-Text Not Available / [Click for Article Request Form](#)**

To investigate the changes of the ischemic lesion in rat brain after subventricular zone (SVZ) cell transplantation and the influence of the grafted cells on the appearance of angiogenesis, SVZ cells, superparamagnetically labeled, were intracisternally transplanted into the rat brain 48 h after onset of embolic stroke. A complete set of magnetic resonance (MR) images was acquired for all animals with (n=8) and without (n=3) cell grafting at approximately 24 h, 72 h, and weekly for 6 weeks after stroke. Transplanted cells were tracked by high-resolution three-dimensional gradient-echo images and the interaction between the cells and ischemic lesion was detected by ISODATA (Iterative Self-Organizing Data Analysis Technique Algorithm) calculated from T(1), T(2) and T(1sat) maps. Tissue status from ISODATA was characterized by a specific signature, which represents the deviation from normal tissue in the feature space. Transplanted SVZ cells selectively migrated towards the ischemic side of the rat brain and approached the lesion boundary within 1-week after grafting. Cell treated rats exhibited a significant reduction of average lesion size compared with control rats (P<0.05). A significant reduction of tissue signature (P<0.001) induced by cell transplantation was localized to the position of grafted cells, and these sites exhibited stably restored cerebral blood flow (CBF) (approximately 85% of normal CBF). Angiogenesis was present in sites either immediately adjacent to or surrounded by the grafted cells. Our data indicate that map-ISODATA accurately and dynamically characterizes the ischemic lesion and its response to cell therapy.

McCord, J. and E. A. Amsterdam (2005). "Newer imaging methods for triaging patients presenting to the emergency department with chest pain." Cardiol Clin **23**(4): 541-8, vii-viii. **Full-Text Not Available / [Click for Article Request Form](#)**

The usefulness of electron beam CT (EBCT) for the risk stratification of patients in the emergency department (ED) who have possible acute coronary syndrome has been evaluated in three small studies. The results of these studies are promising, as patients who have no coronary calcium detected by EBCT essentially had no adverse cardiac events. Although the negative predictive value of EBCT was excellent, the limited positive predictive value that would lead to further diagnostic testing makes this strategy less attractive if applied to a broad population. Further larger studies may help define which patients in the ED who have chest pain and nondiagnostic ECGs can be effectively evaluated by EBCT. Recent advances in noninvasive coronary angiography by multislice computed tomography are of considerable interest in the ED evaluation of patients with undefined chest pain, but the utility of this method in this setting awaits clinical studies.

Nall, C. M. (2006). "Book review." *J Nucl Med Technol* **34**(1): 52. **Full-Text Not Available / [Click for Article Request Form](#)**

Ogunfiditimi, F. (2006). "The role of PAs in robotic-assisted laparoscopic radical prostatectomy." *Jaapa* **19**(3): 57-8, 60-1. **Full-Text Not Available / [Click for Article Request Form](#)**

Patel, O. P. and M. R. Simon (2006). "Oculogyric Dystonic Reaction to Escitalopram with Features of Anaphylaxis Including Response to Epinephrine." *Int Arch Allergy Immunol* **140**(1): 27-29. **Full-Text Not Available / [Click for Article Request Form](#)**

Dystonia-associated features of anaphylaxis, including tongue swelling, and chest and throat tightness, have been rarely reported with selective serotonin reuptake inhibitor (SSRI) use. The patient is a 44-year-old woman who presented with palpitations, diaphoresis, dyspnea, swelling of the lips and tongue, and fixed upward deviation of her right eye following inadvertent ingestion of 20 mg of escitalopram in addition to her usual 10-mg dose. She reported transient resolution of all symptoms after autoinjector aqueous epinephrine administration (0.3 mg), with recurrence of symptoms after 35 min. The patient presented with one prior episode of anaphylactic symptoms and dystonia. She also reported one episode with purely anaphylactic features of swelling of lips and tongue, difficulty breathing and syncope. This case represents a unique dose-dependent episode of escitalopram-associated oculogyric dystonia with anaphylactic features. The transient resolution of the associated features of dystonia with intramuscular epinephrine administration is unique and suggests a common pathophysiology of the dystonic and anaphylactic symptoms.

Peng, H., O. A. Carretero, et al. (2005). "Angiotensin-converting enzyme inhibitors: a new mechanism of action." *Circulation* **112**(16): 2436-45. **[PDF Full-Text](#)**

BACKGROUND: Angiotensin-converting enzyme (ACE) inhibitors are valuable agents for the treatment of hypertension, heart failure, and other cardiovascular and renal diseases. The cardioprotective effects of ACE inhibitors are mediated by blockade of both conversion of angiotensin (Ang) I to Ang II and kinin hydrolysis. Here, we report a novel mechanism that may explain the cardiac antifibrotic effect of ACE inhibition, involving blockade of the hydrolysis of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP). **METHODS AND RESULTS:** To study the role of Ac-SDKP in the therapeutic effects of the ACE inhibitor captopril, we used a model of Ang II-induced hypertension in rats treated with the ACE inhibitor either alone or combined with a blocking monoclonal antibody (mAb) to Ac-SDKP. These hypertensive rats had left ventricular hypertrophy (LVH) as well as increases in cardiac fibrosis, cell proliferation, transforming growth factor-beta (TGF-beta) expression, and phosphorylation of Smad2 (P-Smad2), a signaling mediator of the effects of TGF-beta. The ACE inhibitor did not decrease either blood pressure or LVH; however, it significantly decreased LV collagen from 13.3+/-0.9 to 9.6+/-0.6 microg/mg dry wt (P<0.006), and this effect was blocked by the mAb (12.1+/-0.6; P<0.034, ACE inhibitor versus ACE inhibitor+mAb). In addition, analysis of interstitial collagen volume fraction and perivascular collagen (picrosirius red staining) showed a very similar tendency. Likewise, the ACE inhibitor significantly decreased LV monocyte/macrophage infiltration, cell proliferation, and TGF-beta expression, and these effects were blocked by the mAb. Ang II increased Smad2 phosphorylation 3.2+/-0.9-fold; the ACE inhibitor lowered this to 0.6+/-0.1-fold (P<0.001), and the mAb blocked this decrease to 2.1+/-0.3 (P<0.001, ACE inhibitor versus ACE inhibitor+mAb). Similar findings were seen when the ACE inhibitor was replaced by Ac-SDKP. **CONCLUSIONS:** We concluded that in Ang II-induced hypertension, the cardiac antifibrotic effect of ACE inhibitors is a result of the inhibition of Ac-SDKP hydrolysis, resulting in a decrease in cardiac cell proliferation (probably fibroblasts), inflammatory cell infiltration, TGF-beta expression, Smad2 activation, and collagen deposition.

Rastogi, S., S. Mishra, et al. (2005). "Reversal of maladaptive gene program in left ventricular myocardium of dogs with heart failure following long-term therapy with the Acorn Cardiac Support Device." *Heart Fail Rev* **10**(2): 157-63. **Full-Text Not Available / [Click for Article Request Form](#)**

Progressive left ventricular (LV) dilation is a characteristic feature of heart failure and is associated with poor long-term prognosis. One of the characteristic changes that occur in the failing heart is a change in gene

expression wherein fetal genes that were turned off shortly after birth are re-activated in heart failure and may play a key role in the progressive worsening of the heart failure state. This review discusses reversal of maladaptive gene expression in dogs with chronic heart failure treated long-term with the Acorn Cardiac Support Device (CSD); a passive mechanical device designed to prevent progressive LV enlargement and to restore normal LV chamber geometry. Studies in our laboratories have shown that, in addition to preventing LV dilation and improving LV ejection fraction, long-term therapy with the CSD reverses the maladaptive gene program observed in LV myocardium of dogs with heart failure. Therapy with the CSD was associated with up-regulated mRNA expression for alpha-myosin heavy chain and down-regulated mRNA expression of A- and B- type natriuretic peptides, cytokines and favorably modulated cytoskeletal proteins. These findings provide an explanation for mechanisms that may be partly responsible for the improvement in LV systolic and diastolic function seen in dogs with heart failure after long-term CSD therapy.

Rivard, J. and H. W. Lim (2005). "Ultraviolet phototherapy for pruritus." *Dermatol Ther* **18**(4): 344-54. **Full-Text Not Available** / [Click for Article Request Form](#)

Ultraviolet-based therapy has been used to treat various pruritic conditions including pruritus in chronic renal failure, atopic dermatitis, HIV, aquagenic pruritus and urticaria, solar, chronic, and idiopathic urticaria, urticaria pigmentosa, polycythemia vera, pruritic folliculitis of pregnancy, breast carcinoma skin infiltration, Hodgkin's lymphoma, chronic liver disease, and acquired perforating dermatosis, among others. Various mechanisms of action for phototherapy have been posited. Treatment limitations, side effects, and common dosing protocols are reviewed.

Roth, T., J. K. Walsh, et al. (2005). "An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia." *Sleep Med* **6**(6): 487-95. **Full-Text Not Available** / [Click for Article Request Form](#)

BACKGROUND AND PURPOSE: A double-blind placebo-controlled study of eszopiclone found significant, sustained improvement in sleep and daytime function. The 6-month open-label extension phase is described herein. **PATIENTS AND METHODS:** Adults (21-64) with primary insomnia who reported sleep duration <6.5 h/night or sleep latency >30 min/night were included. Patient-reported endpoints included sleep and daytime function. Safety and compliance were assessed at monthly clinic visits. The final double-blind month was used as the baseline for efficacy analyses of the open-label period. **RESULTS:** Patients who were initially randomized to double-blind placebo and then switched to open-label eszopiclone (n=111) significantly reported the following: (1) decreased sleep latency, wake time after sleep onset, and number of awakenings; (2) increased total sleep time and sleep quality; and (3) improved ratings of daytime ability to function, alertness and sense of physical well-being compared to baseline ($P < 0.0001$ all monthly endpoints). There was no evidence of tolerance on any measure in either group. These subjects (n=360) sustained the double-blind treatment gains for all sleep and daytime parameters, with further significant improvement in a number of measures. Eszopiclone was well tolerated in both groups; unpleasant taste was the only undesirable effect reported by >5% of patients. **CONCLUSIONS:** The significant improvements in sleep and daytime function were evident in those switched from double-blind placebo to 6 months of open-label eszopiclone therapy and were sustained during the 6 months of open-label treatment for those receiving prior double-blind eszopiclone. During 12 months of nightly treatment, eszopiclone 3mg was well tolerated; tolerance was not observed.

Roth, T., K. P. Wright, Jr., et al. (2006). "Effect of tiagabine on sleep in elderly subjects with primary insomnia: a randomized, double-blind, placebo-controlled study." *Sleep* **29**(3): 335-41. [PDF Full-Text](#)

SUBJECT OBJECTIVE: This study further evaluated the effects of tiagabine on sleep in elderly subjects with primary insomnia. **METHODS:** Elderly subjects (aged 65-85 years) meeting DSM-IV-TR criteria for primary insomnia were randomly assigned to receive tiagabine 2, 4, 6, or 8 mg or placebo on 2 consecutive nights. Efficacy was assessed using standard polysomnography and a postsleep questionnaire. Additional assessments included the Assessment of Daily Functioning, Digit Symbol Substitution Test (for residual effects), and visual analog scale (for sleepiness/alertness). **RESULTS:** A total of 207 subjects were randomly assigned to study medication (tiagabine: 2 mg, n = 43; 4 mg, n = 38; 6 mg, n = 45; 8 mg, n = 43; placebo, n = 38). Tiagabine did not significantly effect wake after sleep onset, latency to persistent sleep, or total sleep time compared with placebo ($P > .05$). Significant increases in Stage 3+4 sleep (i.e., slow-wave sleep) were found for tiagabine 4, 6, and 8 mg versus placebo, with a

corresponding significant decrease in Stage 1 sleep ($P < .05$). At 6 and 8 mg, tiagabine also significantly reduced the number of awakenings and increased the ratio of Stage 3+4/(Stage 1 +wake after sleep onset). In general, there were no significant effects on subjects' ratings of sleep or daily functioning with tiagabine 2, 4, and 6 mg versus placebo. These 3 doses had tolerability profiles comparable with that of placebo and were not associated with significant residual effects or reduced alertness. The 8-mg dose, however, significantly decreased subjective total sleep time and refreshing quality of sleep, as well as daily functioning. This dose was associated with troublesome adverse events, significant residual effects, and reduced alertness. CONCLUSIONS: In elderly subjects with primary insomnia, tiagabine did not have a significant effect on wake after sleep onset, latency to persistent sleep, total sleep time, or the subjective rating of sleep. Tiagabine 4, 6, and 8 mg significantly increased slow-wave sleep, with a corresponding significant decrease in Stage 1 sleep. Tiagabine was generally well tolerated, with doses of less than 6 mg having tolerability profiles generally similar to that of placebo. The 8-mg dose, however, was associated with troublesome adverse events, residual effects, and reduced alertness.

Sabbah, H. N. (2005). "Global left ventricular remodeling with the Acorn Cardiac Support Device: hemodynamic and angiographic findings in dogs with heart failure." *Heart Fail Rev* 10(2): 109-15. **Full-Text Not Available / [Click for Article Request Form](#)**

Preventing progressive left ventricular (LV) remodeling is paramount in the treatment of heart failure. In recent years, several surgical approaches have been implemented with the objective of improving LV function through amelioration of progressive LV remodeling. These included surgical reduction of LV size, the so-called Batista procedure, dynamic cardiomyoplasty and mitral valve repair to limit or eliminate functional mitral regurgitation. While the Batista procedure and dynamic cardiomyoplasty have for all practical purposes been abandoned, the lessons learned from these procedures gave rise to a new generation of devices aimed at preventing progressive LV dilation and restoring LV shape by passive mechanical containment of the failing LV. One such device is the Acorn Cardiac Support Device (CSD) or the CorCap. Studies in dogs with intracoronary microembolization-induced moderate and advanced heart failure have shown that long-term monotherapy with the CSD not only prevents progressive LV dilation but, in effect, partially reverses this phenotype. These studies have also shown that the CSD restores, albeit in part, progressive LV chamber sphericity and attenuates functional mitral regurgitation. These benefits were accompanied by improvement in global LV function along with improvements of remodeling at the cellular level. The findings were largely responsible for initiating safety and feasibility clinical trials with the CSD and ultimately, the initiation of the Acorn efficacy trial that was completed in 2004. This review will focus on studies conducted in dogs with heart failure and, specifically on hemodynamic, angiographic and echocardiographic results from these studies that provided support for the CSD as a successful technology targeting "reverse LV remodeling" for the treatment of heart failure.

Sharov, V. G., A. V. Todor, et al. (2005). "Left ventricular histomorphometric findings in dogs with heart failure treated with the Acorn Cardiac Support Device." *Heart Fail Rev* 10(2): 141-7. **Full-Text Not Available / [Click for Article Request Form](#)**

Progressive left ventricular (LV) dilation in the setting of heart failure is associated with increased mortality and morbidity. The Acorn Cardiac Support Device (CSD, Acorn Cardiovascular, Inc., St. Paul, MN) is a preformed polyester device that is surgically placed over the cardiac ventricles, anchored to the AV-groove and tailored anteriorly to fit snugly over the epicardial surface of the heart. The CSD was shown to prevent progressive LV enlargement and, indeed, reduce LV size and attenuate global LV remodeling in both animal models of experimentally-induced heart failure as well as in patients with advanced heart failure. This review will examine the CSD from two histologic perspectives namely, (1) the interaction of the CSD with the epicardial surface of the heart and (2) the effects of long-term therapy with the CSD on cellular remodeling. The review will be based on available pre-clinical data generated in dogs with coronary microembolization-induced heart failure that underwent long-term (3 and 6 months) monotherapy with the CSD. The data will show that long-term implantation leads to encapsulation of the CSD by connective tissue that matures with time and that does not invade the underlying myocardium. Furthermore that implantation of the CSD has no adverse impact on epicardial coronary vessel. At the cellular level, existing data will show that long-term monotherapy with the CSD is associated with reduced cardiomyocyte hypertrophy, reduced volume fraction of replacement and interstitial fibrosis, normalization of capillary density and oxygen diffusion distance and attenuation of cardiomyocyte apoptosis. The outcomes strongly argue in favor of a structural modification of the failing myocardium by CSD therapy that is consistent with "reverse cellular remodeling".

Silva, G., W. H. Beierwaltes, et al. (2006). "Extracellular ATP stimulates NO production in rat thick ascending limb." *Hypertension* **47**(3): 563-7. [PDF Full-Text](#)

NO produced by NO synthase (NOS) 3 acts as an autacoid to regulate NaCl absorption in the thick ascending limb. ATP induces NO production by NOS 3 in endothelial cells. We hypothesized that extracellular ATP activates NOS in thick ascending limbs through P2 receptors. To test this, we measured intracellular NO production using the NO-selective fluorescent dye DAF-2 in suspensions of rat medullary thick ascending limbs. We found that ATP increased DAF-2 fluorescence in a concentration-dependent manner, reaching saturation at &200 micromol/L with an EC50 of 37 micromol/L. The increase was blunted by 74% by the nonselective NOS inhibitor L-omega-nitro-arginine-methyl-ester (2 mmol/L; 60+/-7 versus 16+/-6 arbitrary fluorescence units; P<0.02; n=5). In the presence of the P2 receptor antagonist suramin (300 micromol/L), ATP-induced NO production was reduced by 64% (101+/-11 versus 37+/-5 arbitrary fluorescence units; P<0.002; n=5). Blocking ATP hydrolysis with a 5'-ectonucleotidase inhibitor, ARL67156 (30 micromol/L) enhanced the response to ATP and shifted the EC(50) to 0.8 micromol/L. In the presence of ARL67156, the EC50 of the P2X-selective agonist beta,gamma-methylene-adenosine 5'-triphosphate was 4.8 micromol/L and the EC50 for the P2Y-selective agonist UTP was 40.4 micromol/L. The maximal responses for both agonists were similar. Taken together, these data indicate that ATP stimulates NO production in the thick ascending limb primarily through P2X receptor activation and that ATP hydrolysis may regulate NO production.

Soltanian-Zadeh, H., A. Shahrokni, et al. (2005). "3-D quantification and visualization of vascular structures from confocal microscopic images using skeletonization and voxel-coding." *Comput Biol Med* **35**(9): 791-813. **Full-Text Not Available** / [Click for Article Request Form](#)

This paper presents an image processing approach for information extraction from three-dimensional (3-D) images of vasculature. It extracts quantitative information such as skeleton, length, diameter, and vessel-to-tissue ratio for different vessels as well as their branches. Furthermore, it generates 3-D visualization of vessels based on desired anatomical characteristics such as vessel diameter or 3-D connectivity. Steps of the proposed approach are: (1) pre-processing, (2) distance mappings, (3) branch labeling, (4) quantification, and (5) visualization. We have tested and evaluated the proposed algorithms using simulated images of multi-branch vessels and real confocal microscopic images of the vessels in rat brains. Experimental results illustrate performance of the methods and usefulness of the results for medical image analysis applications.

Xin, H., Y. Li, et al. (2006). "Bone marrow stromal cells induce BMP2/4 production in oxygen-glucose-deprived astrocytes, which promotes an astrocytic phenotype in adult subventricular progenitor cells." *J Neurosci Res*. [PDF Full-Text](#)

Bone morphogenetic proteins (BMPs) affect cell proliferation and differentiation. Astrocytes in ischemic brain are highly responsive to bone marrow stromal cell (BMSC) treatment. We investigated the effects of BMSCs on astrocytes cultured under oxygen- and glucose-deprived conditions, which in part simulate in vivo stroke conditions, to test the hypothesis that BMSCs alter astrocytic expression of BMPs which may contribute to neurological functional recovery of stroke. Quantitative real-time RT-PCR showed that the expression of BMP2/4 mRNAs decreased within ischemic astrocytes, In contrast, BMP2/4 mRNA was significantly increased after cocultured with BMSCs. Western blotting also confirmed this increase at the protein level in the medium of ischemic astrocytes after coculture with BMSCs. As a source of neural stem and progenitor cells, cultured subventricular zone (SVZ) neurospheres exposed to medium obtained from ischemic astrocytes cocultured with BMSCs were significantly enriched in cells expressing the astrocytic marker glial fibrillary acidic protein (GFAP), but not at the expense of beta-III-tubulin-positive SVZ neuroblasts. The expression of BMP2/4 subsequently increased the phosphorylation of downstream effector Smad1 and the expression of notch signal pathway-induced protein Hes1 in cultured SVZ neurospheres. BMP antagonist Noggin blocked the elevation of phosphorylated Smad1 and the expression of Hes1 as well as reducing the percentage of astrocytic SVZ progenitor cells. Our results indicate that BMSCs increase BMP2/4 expression in ischemic astrocytes. These changes enhance subventricular progenitor cell gliogenesis by activating relevant signaling pathways. BMSC-stimulated signaling of endogenous astrocytes may alter the ischemic environment, promoting remodeling of brain and hence, improve functional recovery after stroke.

Zacharek, M. A., P. N. Malani, et al. (2005). "An approach to the diagnosis and management of acute bacterial rhinosinusitis." *Expert Rev Anti Infect Ther* **3**(2): 271-8. **Full-Text Not Available** / [Click for Article Request Form](#)

The management of patients presenting with nasal congestion, rhinorrhea and facial pressure poses a challenge due to the nonspecific nature of these symptoms. A systematic approach to diagnosing acute bacterial rhinosinusitis is essential prior to offering therapies. This review offers an overview of current definitions, diagnostic algorithms and medical therapies available for the management of acute bacterial rhinosinusitis. Antimicrobial use for acute bacterial rhinosinusitis is substantial and carries a major impact on regional resistance patterns.

Zhang, R. L., Z. Zhang, et al. (2006). "Delayed treatment with sildenafil enhances neurogenesis and improves functional recovery in aged rats after focal cerebral ischemia." *J Neurosci Res*. [PDF Full-Text](#)

Increasing age decreases the number of new neurons in the dentate gyrus and the subventricular zone (SVZ). Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, enhances neurogenesis in young rats. The present study tested the hypothesis that sildenafil augments neurogenesis in aged rats after focal cerebral ischemia. Nonischemic aged (18 months, n = 6) Wistar rats exhibited a significant reduction of actively proliferating and relatively quiescent cells in the SVZ measured by the number of minichromosome maintenance protein-2-positive (MCM-2(+)) cells, a marker of the proliferating cells, compared with nonischemic young (3-4 months, n = 8) rats. Occlusion of the middle cerebral artery did not increase the number of MCM-2(+) cells in the SVZ of aged rats at 3 months after focal ischemia. However, treatment with sildenafil at a dose of 3 mg/kg (n = 8) daily for 7 consecutive days starting 7 days after focal ischemia significantly increased the number of MCM-2(+) cells in the SVZ of aged rats compared with aged rats treated with saline (n = 8). Double immunostaining revealed that substantially more Ki67(+) cells (a marker of proliferating cells) were doublecortin(+) (a marker of migrating neuroblasts) in sildenafil-treated than in saline-treated aged animals. In addition, treatment with sildenafil significantly improved functional recovery compared with saline-treated rats. These data suggest that inhibition of PDE5 activity by sildenafil augments neurogenesis in the SVZ of aged ischemic rats, although these rats have reduced numbers of neural progenitor and stem cells in the SVZ.

Zhang, X., F. Jiang, et al. (2005). "Low-dose photodynamic therapy increases endothelial cell proliferation and VEGF expression in nude mice brain." *Lasers Med Sci* **20**(2): 74-9. **Full-Text Not Available** / [Click for Article Request Form](#)

We tested whether low-dose photodynamic therapy (PDT) induces an angiogenic response in the normal brain of nude mice (n=20). Normal brains of nude mice were subjected to PDT at low doses (Photofrin: 2 mg/kg; optical: 2 J/cm² and 4 J/cm²). BrdU (50 mg/kg) was injected (intraperitoneally, i.p.) daily from PDT treatment to sacrifice (1 and 2 weeks after PDT). Laser scanning confocal microscopy, immunohistochemistry, and immunofluorescence staining were performed to assay angiogenic response. Morphological results show no significant tissue damage induced by PDT and two- and three-dimensional image analyses revealed no significant difference in vascular structure between the areas of exposure to PDT and contralateral areas in all mice. However, the number of BrdU immunoreactive cells were significantly increased in the areas of PDT treatment compared with contralateral hemisphere in both groups, and the number of BrdU-positive cells increased in a PDT-dose-dependent manner. Furthermore, immunohistochemical data indicate that PDT at these low doses significantly induces the expression of the vascular endothelial growth factor (VEGF) in PDT-treated regions in the 1-week group, but not in the 2-week group. These data indicate that low-dose PDT results in increased VEGF expression and endothelial cell proliferation in normal brains.