

Henry Ford Health System Publication List

January 2008

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Bagher-Ebadian, H., Q. Jiang, et al. (2008). "A modified fourier-based phase unwrapping algorithm with an application to MRI venography." *J Magn Reson Imaging*. Epub Ahead of Print. [PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, Rochester, Michigan, USA.

PURPOSE: To present a single-step deterministic procedure for unwrapping MRI phase maps. **MATERIALS AND METHODS:** Using an algorithm previously developed for optical applications, Laplacian operators were applied in the Fourier space of the MRI phase map. The original Fourier-based phase unwrapping algorithm was modified so that demodulation accomplished the required signal symmetrization in Fourier space. To evaluate the method's performance in the presence of thermal noise, a set of wrapped phase maps were simulated at different levels of noise in k-space, and the response of the algorithm at different levels of signal-to-noise ratio (SNR) was evaluated for stability. To demonstrate its utility in MRI, the algorithm was applied to the wrapped phase maps of susceptibility-weighted imaging (SWI) studies, which were then used to generate venograms. **RESULTS:** In simulated phase wrapping, the algorithm correctly reproduced the original phase for a wide range of phase gradients and noise. The procedure was fast and produced useful maps of venous structures in SWI images. **CONCLUSION:** A fast and stable single-step deterministic method for unwrapping MRI phase maps is available for such applications as SWI and mapping of static magnetic field inhomogeneity. *J. Magn. Reson. Imaging* 2007. (c) 2007 Wiley-Liss, Inc.

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Cardenas, M. G., K. J. Vigil, et al. (2008). "Prevalence of type 2 diabetes mellitus in patients with primary hyperparathyroidism." *Endocr Pract* **14**(1): 69-75. **Full Text Not Available/Click for Article Request Form**

Department of Internal Medicine, Henry Ford Medical Center, New Center One, 3031 West Grand Boulevard, Suite 800, Detroit, MI 48202-3141, USA.

INTRODUCTION: To determine the prevalence of type 2 diabetes mellitus (DM) in patients with primary hyperparathyroidism. **METHODS:** Prevalence of type 2 DM in 609 patients with surgically verified primary hyperparathyroidism presenting between 1992 and 2003 in a tertiary care hospital setting was assessed retrospectively and compared with published data of type 2 DM prevalence in Michigan's general population. Diagnosis of type 2 DM was made on the basis of documentation in the medical record of fasting or random blood glucose level thresholds according to the 1997 American Diabetes Association criteria, history of diabetes mellitus, or therapy with antidiabetic medications. **RESULTS:** The crude prevalence rate of type 2 DM in patients with primary hyperparathyroidism was significantly higher than the prevalence in the Michigan general population (15.9% vs 7.8%, respectively; $P < .001$). However, this difference was not significant after age stratification except for the age group of 64 to 75 years. Because of the differential distribution of participants across age categories in the 2 groups, a standardized prevalence ratio (SPR) was estimated to account for the variance. After

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adjustment, there was no significant difference in the prevalence of DM between patients with primary hyperparathyroidism and the control population (SPR, 1.19 [95% confidence interval, 0.96-1.45]) except in men. CONCLUSION: The reported higher prevalence of type 2 DM in patients with primary hyperparathyroidism could not be confirmed in this large cohort of patients except for in older patients and in men. Because of the retrospective nature the study and the lack of appropriate controls, further studies are needed to confirm or refute these findings.

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Divi, V. and M. S. Benninger (2006). "Diagnosis and management of laryngopharyngeal reflux disease." *Curr Opin Otolaryngol Head Neck Surg* **14**(3): 124-7. [PDF Full-Text](#)

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PURPOSE OF REVIEW: The recent findings and up-to-date practice guidelines for diagnosing, evaluating, and treating gastro-esophageal reflux disease are discussed. RECENT FINDINGS: The patient complaints for reflux disease are crucial in diagnosis. Although physical examination findings may correlate with laryngopharyngeal reflux, these findings may not improve after an adequate course of treatment. Behavioral modifications are a critical part of improving reflux; however, weight loss has not been shown to improve laryngopharyngeal reflux disease. Patients who used proton-pump inhibitors and histamine blockers were shown to have increased risk of developing Clostridium difficile infections. Laryngopharyngeal reflux has been shown to be a better predictor of Barrett's esophagus than gastroesophageal reflux, although specific screening recommendations have not been determined. SUMMARY: Current studies in laryngopharyngeal reflux demonstrate that improvements in physical examination findings are not a reliable way of determining patient improvement. An empiric trial of therapy is the best diagnostic test for laryngopharyngeal reflux. Future studies will examine the role of transnasal esophagoscopy in the screening of the laryngopharyngeal reflux patient for Barrett's esophagus.

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Eetamadi, A., M. R. Siadat, et al. (2007). "Content-based support environment (C-BASE): Data preparation and similarity measurement." *Proc IEEE Int Conf on Data Mining*: 145-50. **Full Text Not Available/Click for Article Request Form**

Henry Ford Hospital, Department of Neurosurgery

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Eshelman, A. K., S. Mason, et al. (2008). "LVAD destination therapy: applying what we know about psychiatric evaluation and management from cardiac failure and transplant." *Heart Fail Rev*. Epub Ahead of Print. [PDF Full-Text](#)

BioScience, Henry Ford Hospital/CFP6, 2799 West Grand Boulevard, Detroit, MI, 48202, USA, aeshelm1@hfhs.org.

Left ventricular assist devices (LVADs) have evolved into long-term use as destination therapy for those with severe end-stage heart failure due to other medical risks. Success with LVAD depends on adherence to a complicated mechanical regimen, and acceptance of a life that is far from normal. Patients with LVADs share characteristics with other end-stage cardiac failure patients and those waiting for or receiving heart transplants. Understanding the more thoroughly studied issues of psychiatric disorders, adherence, and behavioral correlates of success in heart failure and transplantation may identify feasible strategies for optimizing care of LVAD patients and suggest directions for future research. Depression and distress complicate post-transplant care. Psychiatric morbidity is associated with poor outcomes, including graft rejection, non-adherence, hospitalizations, infection, and death. With a high risk of embolic neurological events, patients' ability for self-care may be compromised. Psychiatric symptoms are underdiagnosed and undertreated, which may impact overall survival and quality of life.

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Field, E., H. M. Horst, et al. (2008). "Hyperbilirubinemia: a risk factor for infection in the surgical intensive care unit." *Am J Surg*. Epub Ahead of Print. **Full Text Not Available/Click for Article Request Form**

Department of Surgery, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: Hyperbilirubinemia in intensive care unit (ICU) patients is common. We hypothesized that hyperbilirubinemia in the surgical ICU predisposes patients to infection. METHODS: Patients with bilirubin ≤ 3 mg/dL were compared to patients with bilirubin > 3 mg/dL. We then compared the low bilirubin patients to high bilirubin patients who developed infection after their hyperbilirubinemia. RESULTS: There were 1,620 infections in 5,712 patients with low bilirubin (28%), compared with 284 in 409 patients in the high bilirubin group (69%, $P < .001$). After removing the patients in whom hyperbilirubinemia developed after infection, we found infection in 156 of 281 remaining patients (56%, $P < .001$). This group had a 3-fold increased risk of infection compared with low bilirubin (odds ratio [OR] 3.17, 95% confidence interval [CI] 2.48-4.03, $P < .001$). CONCLUSIONS: There is an increased susceptibility to infection among jaundiced surgical ICU (SICU) patients that persists even when sepsis-related hyperbilirubinemia patients are excluded.

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Jafari-Khouzani, K., H. Soltanian-Zadeh, et al. (2007). "Hippocampal volume and texture analysis for temporal lobe epilepsy." *Proc IEEE* 394-7. **Full Text Not Available/Click for Article Request Form**

Henry Ford Hospital, Department of Neurosurgery

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Jain, R., S. K. Ellika, et al. (2008). "Quantitative Estimation of Permeability Surface-Area Product in Astroglial Brain Tumors Using Perfusion CT and Correlation with Histopathologic Grade." *AJNR Am J Neuroradiol*. Epub Ahead of Print. **PDF Full-Text**

Division of Neuroradiology, Departments of Radiology, Neurosurgery, Biostatistics and Research Epidemiology, Pathology, and Neurology, Henry Ford Hospital, Detroit, Mich.

BACKGROUND AND PURPOSE: Glioma angiogenesis and its different hemodynamic features, which can be evaluated by using perfusion CT (PCT) imaging of the brain, have been correlated with the grade and the aggressiveness of gliomas. Our hypothesis was that quantitative estimation of permeability surface area product (PS), cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) in astroglial brain tumors by using PCT will correlate with glioma grade. High-grade gliomas will show higher PS and CBV as compared with low-grade gliomas. MATERIALS AND METHODS: PCT was performed in 32 patients with previously untreated astroglial tumors (24 high-grade gliomas and 8 low-grade gliomas) by using a total acquisition time of 170 seconds. World Health Organization (WHO) glioma grades were compared with PCT parameter absolute values by using Student or nonparametric Wilcoxon 2-sample tests. Receiver operating characteristic (ROC) analyses were also done for each of the parameters. RESULTS: The differences in PS, CBV, and CBF between the low- and high-grade tumor groups were statistically significant, with the low-grade group showing lower mean values than the high-grade group. ROC analyses showed that both CBV (C-statistic 0.930) and PS (C-statistic 0.927) were very similar to each other in differentiating low- and high-grade gliomas and had higher predictability compared with CBF and MTT. Within the high-grade group, differentiation of WHO grade III and IV gliomas was also possible by using PCT parameters, and PS showed the highest C-statistic value (0.926) for the ROC analyses in this regard. CONCLUSIONS: Both PS and CBV showed strong association with glioma grading, high-grade gliomas showing higher PS and CBV as compared with low-grade gliomas. Perfusion parameters, especially PS, can also be used to differentiate WHO grade III from grade IV in the high-grade tumor group.

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Jiang, F., X. Zhang, et al. (2008). "Combination therapy with antiangiogenic treatment and photodynamic therapy for the nude mouse bearing u87 glioblastoma." *Photochem Photobiol* **84**(1): 128-37. **Full Text Not Available/Click for Article Request Form**

Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.

The objective of this study was to evaluate the effects of combination therapy with photodynamic therapy (PDT) and a novel antiangiogenic regimen using monoclonal antibodies against both vascular endothelial growth factor receptors (VEGFR)-1 (MF1) and VEGFR-2 (DC101) on intracranial glioblastoma xenografts in nude mice. Nude mice bearing intracerebral U87 glioblastoma were treated with PDT and the antiangiogenic regimen (MF1 and DC101) either alone or in combination, while those left untreated served as tumor controls. Tumor volume and animal survival time were analyzed to evaluate the outcome of different treatment modalities. In addition, the immunohistochemical expression of VEGF in the brain adjacent to the tumor, von Willebrand factor (vWF), apoptotic, and proliferative markers in the tumor area were examined. PDT or MF1 + DC101 alone significantly reduced the tumor volume and prolonged the survival time of glioma-implanted animals. Combined therapy markedly reduced tumor volume and increased survival time with significantly better outcomes than both monotherapies. Both vWF and VEGF levels significantly increased after PDT while they both significantly decreased after antiangiogenic treatment, compared with no treatment. PDT plus antiangiogenic treatment led to significant decreases in both vWF and VEGF expression, compared with PDT alone. Either PDT or antiangiogenic treatment alone significantly increased tumor cell apoptosis compared with no treatment, while combination therapy resulted in further augmentation of apoptosis. Antiangiogenic treatment with or without PDT significantly decreased tumor cell proliferation, compared with either no treatment or PDT alone. In summary, we demonstrate both significant inhibition of tumor growth and extended survival of mice treated by the combination therapy with PDT and antiangiogenic agents, compared with each single treatment, suggesting that the combination therapy may be a promising strategy to improve clinical outcomes in glioblastoma.

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Kanjanauthai, S. and T. Kanluen (2007). "*Community-acquired Klebsiella oxytoca causing splenic abscess.*" Int J Infect Dis. Epub Ahead of Print. **Full Text Not Available/Click for Article Request Form**

Department of Internal Medicine, Henry Ford Hospital, 2799 West Grand Blvd, CFP-1, Detroit, MI 48202, USA.

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Kanjanauthai, S. and T. Kanluen (2008). "*Propionibacterium acnes: A rare cause of late prosthetic valve endocarditis and aortic root abscess.*" Int J Cardiol. Epub Ahead of Print. [PDF Full-Text](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, United States.

Propionibacterium acnes is an anaerobic, non-spore forming, gram-positive bacillus, and is often part of the normal flora of human skin. It usually has relatively low virulence. However, it can rarely cause serious infections including infections of prosthetic valves, native valves, and annuloplasty rings. We describe a rare case of late prosthetic aortic valve endocarditis and aortic root abscess caused by *P. acnes*, an easily ignored pathogen.

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Kim, J. H., S. L. Brown, et al. (2008). "*Mechanisms of radiation-induced brain toxicity and implications for future clinical trials.*" J Neurooncol. Epub Ahead of Print. [PDF Full-Text](#)

Department of Radiation Oncology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI, 48025, USA, sryu1@hfhs.org.

Radiation therapy is widely used in the treatment of primary malignant brain tumors and metastatic tumors of the brain with either curative or palliative intent. The limitation of cancer radiation therapy does not derive from the inability to ablate tumor, but rather to do so without excessively damaging the patient. Among the varieties of radiation-induced brain toxicities, it is the late delayed effects that lead to severe and irreversible neurological consequences. Following radiation exposure, late delayed effects within the CNS have been attributable to both parenchymal and vascular damage involving oligodendrocytes, neural progenitors, and endothelial cells. These reflect a dynamic process involving radiation-induced death of target cells and subsequent secondary reactive neuroinflammatory processes that are believed to lead to selective cell loss, tissue damage, and functional deficits. The progressive, late delayed damage to the brain after high-dose radiation is thought to be caused by radiation-induced long-lived free radicals, reactive oxygen species, and pro-inflammatory

cytokines. Experimental studies suggest that radiation-induced brain injury can be successfully mitigated and treated with several well established drugs in wide clinical use which exert their effects by blocking pro-inflammatory cytokines and reactive oxygen species. This review highlights preclinical and early clinical data that are translatable for future clinical trials.

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Klausner, H. A., P. Brown, et al. (2007). "A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis." *Curr Med Res Opin* **23**(11): 2637-45. **Full Text Not Available/Click for Article Request Form**

Henry Ford Hospital, Detroit, MI, USA.

OBJECTIVE: A double-blind, noninferiority trial was conducted to establish the safety and efficacy of a once-daily, 5-day course of levofloxacin 750 mg compared to a twice-daily, 10-day course of ciprofloxacin in complicated urinary tract infections (cUTI) and acute pyelonephritis (AP). This report focuses on subjects with AP. RESEARCH DESIGN AND METHODS: Adult male and female subjects with clinical signs and symptoms of AP and laboratory confirmation of their diagnosis were randomized to receive one dose of levofloxacin 750 mg once daily intravenously (i.v.) or orally and one dose of placebo for 5 days, followed by placebo; or ciprofloxacin 400 mg i.v. and/or 500 mg orally twice daily for 10 days. MAIN OUTCOME MEASURES: The primary, prospectively defined end point was microbiologic eradication at post-therapy (study days 15-22). Secondary outcomes included clinical response and safety and tolerability. RESULTS: In the modified intent-to-treat (mITT) population (levofloxacin 94, ciprofloxacin 98), 83% of levofloxacin-treated and 79.6% of ciprofloxacin-treated subjects achieved microbiological eradication (difference -3.4, 95% CI -14.4%, 7.6%). In the microbiologically evaluable (ME) population (levofloxacin 80, ciprofloxacin 76), 92.5% of levofloxacin-treated vs. 93.4% of ciprofloxacin-treated subjects (difference -0.9, 95% CI -7.1%, 8.9%) achieved microbiologic eradication. Clinical success was achieved in 86.2% vs. 80.6% (mITT) and in 92.5% vs. 89.5% (ME) of levofloxacin-treated and ciprofloxacin-treated subjects, respectively. *Escherichia coli* was the most commonly isolated uropathogen. Few (2.1%) of the pathogens were fluoroquinolone-resistant. Adverse events (AEs) were similar to those seen previously with both agents. Potential limitations are that this analysis is based on a subset of subjects from a larger study and, because of different durations of therapy, the results may be biased against levofloxacin. CONCLUSIONS: High-dose, short-course therapy with levofloxacin in subjects with AP is at least as effective as standard 10-day therapy with ciprofloxacin.

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Krishnamurthy, S., J. P. Kelleher, et al. (2007). "Effects of tobacco dose and length of exposure on delayed neurological deterioration and overall clinical outcome after aneurysmal subarachnoid hemorrhage." *Neurosurgery* **61**(3): 475-80; discussion 480-1. [PDF Full-Text](#)

Department of Neurosurgery, State University of New York, Upstate Medical University, Syracuse, New York, USA.

OBJECTIVE: The association between smoking and intracranial aneurysms is now well recognized. However, the relationship between tobacco use and outcome after aneurysmal subarachnoid hemorrhage (SAH) is not as well understood and published results are contradictory. The purpose of this study is to examine the degree to which the amount of tobacco exposure/dose impacts delayed neurological deterioration and overall clinical outcome after aneurysmal SAH. METHODS: We reviewed our retrospective database of patients with aneurysmal SAH. We assessed the impact of four independent tobacco variables: smoker (ever smoked), current smoker (actively smoking within the past yr and with at least a 10 pack per yr history of smoking), long-term smoker (at least a 20 pack per yr history), and salient (combination of current and long-term) smoker as well as tobacco dose (categorized according to number of packs per yr) on two outcome variables, delayed neurological deterioration and dichotomized Glasgow Outcome Scale score. Covariates included in the analysis were age, sex, Hunt and Hess grade, Fisher grade, and medical comorbidities. Stepwise elimination with logistic regression was used to arrive at a final multivariate model for each outcome and independent tobacco variable in the presence of covariates. RESULTS: A total of 320 patients were analyzed. As expected, Hunt and Hess grade was a significant predictor of both delayed neurological deterioration and clinical outcome. Tobacco use (smoker variable) showed an independent association with the development of delayed neurological deterioration ($P = 0.0409$; odds ratio, 1.78; 95% confidence interval, 1.02-3.08). In addition, patients who were long-term or current smokers (salient smoker variable) showed a trend toward a slightly stronger association with the occurrence of delayed neurological deterioration ($P = 0.0229$; odds ratio, 1.85;

95% confidence interval, 1.09-3.14). No tobacco use variable was associated with clinical outcome (Glasgow Outcome Scale) in the multivariate analysis. CONCLUSION: The duration and timing of tobacco use, rather than the dose of tobacco per se, seem to be risk factors for delayed neurological deterioration after aneurysmal SAH. Although we did not find an association between tobacco use and overall clinical outcome after aneurysmal SAH, these results suggest that the distribution of various patterns of tobacco use within a given data set may influence the overall results.

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Maltsev, V. A., V. Reznikov, et al. (2008). "Modulation of the late sodium current by Ca^{2+} , calmodulin, and CaMKII in normal and failing dog cardiomyocytes: similarities and differences." *Am J Physiol Heart Circ Physiol*. Epub Ahead of Print. [PDF Full-Text](#)

Internal Medicine, Henry Ford Hospital, Detroit, Michigan, United States.

Augmented and slowed late Na^{+} current (INaL) was implicated in action potential duration variability, early afterdepolarizations, and abnormal Ca^{2+} handling in human and canine failing myocardium. Objective was to study INaL modulation by cytosolic Ca^{2+} ($[Ca^{2+}]_i$) in normal and failing ventricular myocytes. Methods: Chronic heart failure was produced in 10 dogs by intracoronary microembolizations, 6 normal dogs served as a control. INaL fine structure was measured by whole-cell patch-clamp in ventricular myocytes and approximated by a sum of fast and slow exponentials produced by burst and late scattered modes of Na^{+} channel gating, respectively. Results: INaL greatly enhanced as $[Ca^{2+}]_i$ increased from "free" to 1 μM : its maximum density increased, decay of both exponentials slowed, and steady-state-inactivation curve (SSI) shifted towards more positive potentials. Testing inhibition of CaMKII and CaM revealed similarities and differences of INaL modulation in failing vs. normal myocytes. Similarities: 1) CaMKII slows INaL decay and decreases the amplitude of fast exponential; 2) Ca^{2+} shifts SSI rightward. Differences: 1) slowing INaL by CaMKII is greater; 2) CaM shifts SSI leftward; 3) Ca^{2+} increases the amplitude of slow exponential. Conclusions: Ca^{2+} /CaM/CaMKII signaling increases INaL and Na^{+} influx in both normal and failing myocytes by slowing kinetics and shifting SSI. This Na^{+} influx provides a novel Ca^{2+} positive feedback mechanism (via Na^{+} / Ca^{2+} exchanger), enhancing contractions at higher beating rates, but worsening cardiomyocytes contractile and electrical performance in conditions of poor Ca^{2+} handling in heart failure. Key words: heart failure, sodium channel, calcium, arrhythmia.

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Monaghan, K. G., G. L. Feldman, et al. (2008). "Technical standards and guidelines for reproductive screening in the Ashkenazi Jewish population." *Genet Med* **10**(1): 57-72. [PDF Full-Text](#)

Department of Medical Genetics, Henry Ford Hospital, Detroit, Michigan, USA.

DISCLAIMER: These Technical Standards and Guidelines were developed primarily as an educational resource for clinical laboratory geneticists to help them provide quality clinical laboratory genetic services. Adherence to these standards and guidelines is voluntary and does not necessarily assure a successful medical outcome. These Standards and Guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinical laboratory geneticist should apply his or her own professional judgment to the specific circumstances presented by the individual patient or specimen. Clinical laboratory geneticists are encouraged to document in the patient's record the rationale for the use of a particular procedure or test, whether or not it is in conformance with these Standards and Guidelines. They also are advised to take notice of the date any particular standard or guidelines was adopted, and to consider other relevant medical and scientific information that becomes available after that date.

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Nagaraja, T. N., K. Karki, et al. (2008). "Identification of variations in blood-brain barrier opening after cerebral ischemia by dual contrast-enhanced magnetic resonance imaging and T1sat measurements." *Stroke* **39**(2): 427-32. [PDF Full-Text](#)

Department of Anesthesiology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA. annta@neuro.hfh.edu

BACKGROUND AND PURPOSE: Variations in blood-brain barrier (BBB) opening after ischemia have been suggested by some tracer and magnetization transfer studies, although direct in vivo proof is still lacking. Contrast-enhanced magnetic resonance imaging (MRI) is also often used to visualize BBB damage in stroke. We hypothesized that MR contrast agents of different sizes enhance differently when BBB openings vary in size and that magnetization transfer alterations, measured by T(1) in the presence of off-resonance radiofrequency saturation (T(1sat)), in these regions reflect such differences. **METHODS:** Male Wistar rats (approximately 300 g, n=7) were subjected to 3 hours of suture occlusion of the middle cerebral artery followed by reperfusion. Status of the BBB at 24 hours after the ictus was assessed first by Gd-DTPA (554 Da) MRI and then by Gd-bovine serum albumin linked to Evans blue (Gd-BSA-EB; approximately 68 kDa) MRI for contrast enhancement; T(1sat) changes, cerebral blood flow, and blood-to-brain transfer constants (K(i)s) for the 2 contrast agents were measured. After MRI, rats were injected with fluorescent dextran and brains were studied by fluorescence microscopy. **RESULTS:** The Gd-BSA-EB-enhancing areas were always smaller (147+/-80 pixels) than those for Gd-DTPA (308+/-204 pixels) and were contained within the latter. The difference between the 2 areas was significant (P=0.024). Changes in T(1sat) were larger in Gd-BSA-EB-enhancing areas (ipsilateral to contralateral [I/C]=1.53+/-0.20) than in Gd-DTPA-enhancing areas (I/C=1.40+/-0.24, P=0.005). The differences in cerebral blood flow values between the 2 regions were not significant (P=0.62), but those for the K(i) values of the 2 tracers were different (P=0.01 to 0.02). Excellent agreement between regions of Gd-BSA-EB enhancement and EB fluorescence was also observed. **CONCLUSIONS:** These results substantiate earlier reports of regional differences in BBB opening after stroke and provide the first in vivo evidence for this phenomenon. They also support the possible use of T(1sat) in quantifying stroke-induced graded BBB damage in the absence of contrast-enhanced MRI.

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Paz, N., E. Y. Levanon, et al. (2007). "Altered adenosine-to-inosine RNA editing in human cancer." *Genome Res* **17**(11): 1586-95. **Full Text Not Available/Click for Article Request Form**

Cancer Research Center, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

Adenosine-to-inosine (A-to-I) RNA editing was recently shown to be abundant in the human transcriptome, affecting thousands of genes. Employing a bioinformatic approach, we identified significant global hypoeediting of Alu repetitive elements in brain, prostate, lung, kidney, and testis tumors. Experimental validation confirmed this finding, showing significantly reduced editing in Alu sequences within MED13 transcripts in brain tissues. Looking at editing of specific recoding and noncoding sites, including in cancer-related genes, a more complex picture emerged, with a gene-specific editing pattern in tumors vs. normal tissues. Additionally, we found reduced RNA levels of all three editing mediating enzymes, ADAR, ADARB1, and ADARB2, in brain tumors. The reduction of ADARB2 correlated with the grade of malignancy of glioblastoma multiforme, the most aggressive of brain tumors, displaying a 99% decrease in ADARB2 RNA levels. Consistently, overexpression of ADAR and ADARB1 in the U87 glioblastoma multiforme cell line resulted in decreased proliferation rate, suggesting that reduced A-to-I editing in brain tumors is involved in the pathogenesis of cancer. Altered epigenetic control was recently shown to play a central role in oncogenesis. We suggest that A-to-I RNA editing may serve as an additional epigenetic mechanism relevant to cancer development and progression.

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Qian, J. Y., P. Harding, et al. (2008). "Reduced cardiac remodeling and function in cardiac-specific EP4 receptor knockout mice with myocardial infarction." *Hypertension* **51**(2): 560-6. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202-2689, USA.

We have shown previously that cyclooxygenase-2 inhibition reduces cardiac hypertrophy and fibrosis postmyocardial infarction (MI) in a mouse model and that prostaglandin E(2) stimulates cardiomyocyte hypertrophy in vitro through its EP(4) receptor. Because the role of cardiac myocyte EP(4) in cardiac function and hypertrophy in vivo is unknown, we generated mice lacking EP(4) only in cardiomyocytes (CM- EP(4) knockout [KO]). Twelve- to 14-week-old mice were evaluated using echocardiography and histology. There were no differences in ejection fraction, myocyte cross-sectional area, and interstitial collagen fraction between KO mice and littermate controls. To test the hypothesis that EP(4) is involved in cardiac remodeling after MI, we induced MI by ligating the left anterior descending coronary artery. Two weeks later, the mice were subjected to echocardiography, and hearts were removed for histology and Western blot. There was no difference in infarct size between KO mice and controls; however, KO mice showed less myocyte cross-sectional area and interstitial collagen fraction than controls. Also, CM-EP4 KO mice had reduced ejection fraction. Because the transcription factor Stat-3

is involved in hypertrophy and protection from ischemic injury, we tested whether it was activated in control and KO mouse hearts after MI. Western blot indicated that Stat-3 was activated in control hearts after MI but not in KO hearts. Thus, CM-EP4 deletion decreased hypertrophy, fibrosis, and activation of Stat-3. However, cardiac function was unexpectedly worsened in these mice. We conclude that cardiac myocyte EP(4) plays a role in hypertrophy via activation of Stat-3, a process that seems to be cardioprotective.

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Ryu, S., R. Jin, et al. (2008). "Pain Control by Image-Guided Radiosurgery for Solitary Spinal Metastasis." *J Pain Symptom Manage*. Epub Ahead of Print. [PDF Full-Text](#)

Departments of Radiation Oncology (S.R., R.J., J.-Y.J., Q.C., B.M.), Neurosurgery (S.R., J.R.), and Medical Oncology (J.A.), Henry Ford Hospital, Detroit, Michigan, USA.

Precision and accuracy of image-guided spinal radiosurgery has been previously demonstrated. This study was carried out to determine the clinical efficacy of spine radiosurgery for the treatment of solitary spinal metastases with or without cord compression. A total of 49 patients with 61 separate spinal metastases were treated with radiosurgery. All patients had pathologically proven primary cancers and had either synchronous or metachronous metastasis to the spine. The majority of the patients presented with back pain. All patients received single-dose radiosurgery to the involved spine only. The radiosurgery dose ranged from 10 to 16Gy. The primary endpoint was pain control, but outcomes in neurological status and radiological tumor control also were assessed. The median time to pain relief was 14 days and the earliest time of pain relief was within 24hours. Complete pain relief was achieved in 46%, partial relief in 18.9%, and stable symptoms in 16.2%. Relapse of pain at the treated spinal segment was 6.9%. Median duration of pain relief at the treated spine was 13.3 months. Overall pain control rate for 1 year was 84%. This experience demonstrates that spinal radiosurgery can achieve rapid and durable pain relief. Single-dose radiosurgery has a potential to be a viable treatment option for single spinal metastasis.

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Sharma, U., N. E. Rhaleb, et al. (2008). "Novel anti-inflammatory mechanisms of N-Acetyl-Ser-Asp-Lys-Pro in hypertension-induced target organ damage." *Am J Physiol Heart Circ Physiol*. Epub Ahead of Print. [PDF Full-Text](#)

Internal Medicine, Henry Ford Hospital, Hypertension and Vascular Research, Detroit, Michigan, United States.

Background: High blood pressure (HBP) is an important risk factor for cardiac, renal and vascular dysfunction. Excess inflammation is the major pathogenic mechanism for HBP-induced target organ damage (TOD). N-acetyl-Ser-Asp-Lys-Pro (Ac-SDKP), a tetrapeptide specifically degraded by angiotensin converting enzyme (ACE), reduces inflammation, fibrosis and TOD induced by high blood pressure. Hypothesis: Ac-SDKP exerts its anti-inflammatory effects by inhibiting: 1) differentiation of bone marrow stem cells (BMSC) to macrophages, 2) activation and migration of macrophages and 3) release of the pro-inflammatory cytokine TNF-alpha by activated macrophages. Methods: BMSC were freshly isolated from mouse tibias and femurs. Differentiation of murine BMSC to macrophages was analyzed by flow cytometry using F4/80 as a marker of macrophage maturation. Macrophage migration was measured in a modified Boyden chamber. TNF-alpha release by activated macrophages was measured by enzyme-linked immunosorbent assay (ELISA). Myocardial macrophage activation in Angiotensin-II (Ang II) treated mice was detected by Western blotting of Mac-2 (galectin-3) protein. Interstitial collagen deposition was measured by Picosirius red staining. Results: Ac-SDKP (10 nM) reduced differentiation of cultured BMSC to mature macrophages by 24.5% [F4/80 positivity: 14.09 +/- 1.06 mean fluorescent intensity (MFI) for vehicle and 10.63 +/- 0.35 for Ac-SDKP; p < 0.05]. Ac-SDKP also decreased galectin-3 and macrophage colony-stimulating factor (M-CSF)-dependent macrophage migration. In addition, Ac-SDKP decreased secretion of TNF-alpha by macrophages stimulated with bacterial LPS. In Ang II-treated hypertensive mice, Ac-SDKP reduced expression of galectin-3, a protein produced by infiltrating macrophages in the myocardium and interstitial collagen deposition. Conclusion: This study demonstrates that part of the anti-inflammatory effect of Ac-SDKP is due to its direct effect on BMSC differentiation and macrophage activation, reinforcing the protective properties of Ac-SDKP in high blood pressure-induced inflammation and organ damage. Key words: Ac-SDKP, macrophages, inflammation, activation, AngII hypertension.

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Tchernenko, V., H. R. Halvorson, et al. (2008). "DNA bubble formation in transcription initiation." *Biochemistry* **47**(7): 1871-84. **Full Text Not Available/Click for Article Request Form**

Molecular Biology Section, Bone and Joint Center, Henry Ford Hospital, Detroit, Michigan 48202, and Molecular Mechanisms of Transcription Section, NCI Center for Cancer Research, Frederick Cancer Research and Development Center, Frederick, Maryland 27102.

The properties of the DNA bubble in the transcription open complex have been characterized by topological analysis of DNA circles containing the lac UV5 promoter or the PR promoter from bacteriophage lambda. Topological analysis is particularly well suited to this purpose since it quantifies the changes in DNA duplex geometry caused by bubble formation as well as by superhelical DNA wrapping. The duplex unwinding that results from bubble formation is detected as a reduction in topological linking number of the DNA circle, and the precision of this measurement has been enhanced in the current study through the use of 8 or 10 promoter copies per circle. Several lines of evidence indicate that the linking number change induced by open complex formation is essentially all due to bubble generation, with very little derived from superhelical wrapping. Accordingly, the linking number change of -1.17 measured for the lac UV5 promoter indicates that the size of the lac UV5 bubble is about 12.3 base pairs, while the change of -0.98 measured for the lambda PR promoter indicates that the lambda PR bubble is 10.3 base pairs. It was also found that the presence or absence of magnesium ion had little effect on the value of the linking number change, a result that resolves the uncertainty associated with use of chemical probes to study the effect of magnesium on bubble size. Finally, the magnitude of linking number change increases progressively when the 3' end of a transcript is extended to +2 and +3 in an abortive initiation complex. This indicates that the transcription bubble expands at its leading edge in the abortive complex, results that confirm and extend the proposal of a DNA "scrunching" mechanism at the onset of transcription. These results are relevant to several models for the structure of DNA in the functional open complex in solution, and provide an important complement to the structural information available from recent crystal structures.

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Tchernenko, V., M. Radlinska, et al. (2008). "DNA bending in transcription initiation." *Biochemistry* **47**(7): 1885-95. **Full Text Not Available/Click for Article Request Form**

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Electrophoretic mobility shift (bandshift) phasing analysis and rotational variant topological analysis were performed on initiation complexes formed on the bacteriophage lambda PR promoter. Both the open complex and an abortive complex containing a short RNA primer extending to +3 were characterized. The two methods were used to analyze a series of constructs containing tandemly repeated copies of the PR promoter, with the repeat length increased in single base pair increments to progressively change the rotational setting of adjacent copies. The phasing effect observed in bandshift analysis of open complexes formed on this set of constructs provided qualitative evidence for the presence of a bend. Subsequent rotational variant topological analysis confirmed this and quantified the overall bend angle in the open complex as well as in the +3 abortive complex: a bend of 49 degrees +/- 7 degrees was measured for the open complex, while a bend of 47 degrees +/- 11 degrees was measured for the +3 complex, i.e., the two bends are the same. However, the topological results are not consistent with extensive superhelical wrapping of DNA on either complex as has been proposed. The two complexes do differ in the size of the transcription bubble: the open complex contains a 10.4 +/- 0.1 bp bubble, while that of the +3 complex is 12.2 +/- 0.1 bp, a result consistent with "DNA scrunching" during the onset of transcription. A model for the overall path of the DNA in the open complex is presented that is consistent with the measured bend angle. Measurement of both bubble size and overall bend angle complements the results of crystal structures in providing an enhanced description of the solution structures of the intact initiation complexes.

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Vajda, P. (2007). "Prehospital care of the adult trauma patient." *Bratisl Lek Listy* **108**(8): 371-4. **Full Text Not Available/Click for Article Request Form**

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The concept of emergency medical transport originated from the need to move wounded soldiers from the battlefield to aid stations and other medical facilities (Ref. 11). Full Text (Free, PDF) www.bmj.sk.

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Varelas, P. N., L. Schultz, et al. (2008). "*The Impact of a Neuro-Intensivist on Patients with Stroke Admitted to a Neurosciences Intensive Care Unit.*" Neurocrit Care. Epub Ahead of Print. **Full Text Not Available/Click for Article Request Form**

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INTRODUCTION: Stroke Units improve the outcome in patients with mild to moderate severity strokes. We sought to examine the role that a full-time neurointensivist (NI) might play on the outcomes of patients with more severe strokes admitted to a Neurosciences Intensive Care Unit (NICU). METHODS: Data regarding 433 stroke patients admitted to a 10-bed university hospital NICU were prospectively collected in two 19-month periods, before and after the appointment of a NI. Outcomes and disposition of patients with ischemic stroke (IS), intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) were compared between the two periods, using univariate and multivariate analyses. RESULTS: One hundred and seventy-four patients with strokes were admitted in the period before and 259 in the period after the NI. Observed mortality did not differ between the two periods. More patients were discharged home in the after period (75% vs. 54% in the before period ($P = 0.003$)). After adjusting for covariates, the NICU and hospital LOS were shorter for each type of stroke in the after period (Cox proportional hazard ratios, 95% CI were 2.37, 1.4-4.1 and 1.8, 1.04-3 for IS, 1.98, 1.3-3 and 1.2, 0.8-1.9 for ICH, and 1.6, 1.1-2.3 and 1.4, 1.01-2 for SAH, respectively) or for all strokes (1.92, 1.52-2.43 and 1.7, 1.28-2.25 for the first 12 days of hospital admission). CONCLUSION: The direct patient care offered and the organizational changes implemented by a NI shortened the NICU and hospital LOS and improved the disposition of patients with strokes admitted to a NICU.

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Yeni, Y. N., E. A. Zelman, et al. (2007). "*Trabecular shear stress amplification and variability in human vertebral cancellous bone: Relationship with age, gender, spine level and trabecular architecture.*" Bone. Epub Ahead of Print. [PDF Full-Text](#)

Bone and Joint Center, Henry Ford Hospital, Detroit, MI, USA.

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Yerramshetty, J. S. and O. Akkus (2007). "*The associations between mineral crystallinity and the mechanical properties of human cortical bone.*" Bone. Epub Ahead of Print. [PDF Full-Text](#)

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It is well known that the amount of mineralization renders bone its stiffness. However, besides the mere amount of the mineral phase, size and shape of carbonated apatite crystals are postulated to affect the mechanical properties of bone tissue as predicted by composite mechanics models. Despite this predictive evidence, there is little experimental insight on the relation between the characteristics of mineral crystals and hard tissue mechanics. In this study, Raman spectroscopy was used to provide information on the crystallinity of bone's mineral phase, a parameter which is an overall indicator of mineral crystal size and stoichiometric perfection. Raman scans and mechanical tests (monotonic and fatigue; $n=64$ each) were performed on the anterior, medial, lateral and posterior quadrant sections of 16 human cadaveric femurs (52 y.o.-85 y.o.). The reported coefficient of determination values (R^2) were adjusted for the effects of age to bring out the unbiased contribution of crystallinity. Crystallinity was able to explain 6.7% to 48.3% of the variation in monotonic mechanical properties. Results indicated that the tissue-level strength and stiffness increased with increasing crystallinity while the ductility reduced. Crystallinity explained 11.3% to 63.5% of the variation in fatigue properties. Moduli of specimens with greater crystallinity degraded at a slower rate and, also, they had longer fatigue lives. However, not every anatomical quadrant displayed these relationships. In conclusion, these results acknowledge crystal properties as an important bone quality factor and raise the possibility that aberrations in these properties may contribute to senile osteoporotic fractures.

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Zhang, J., Y. Li, et al. (2008). "Bone marrow stromal cells protect oligodendrocytes from oxygen-glucose deprivation injury." *J Neurosci Res*. Epub Ahead of Print. [PDF Full-Text](#)

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Oligodendrocyte (OLG) damage leads to demyelination, which is frequently observed in ischemic cerebrovascular diseases. In this study, we investigated the effect of bone marrow stromal cells (BMSCs) on OLGs subjected to oxygen-glucose deprivation (OGD). N20.1 cells (mouse OLG cell line) were transferred into an anaerobic chamber for 3 hr in glucose-free and serum-free medium. After OGD incubation, OLG cultures were divided into the following groups: 1) OGD alone, 2) OLG cocultured with BMSCs, 3) treatment with the phosphoinositide 3-kinase (PI3k) inhibitor LY294002, 4) LY294002-treated OLGs with BMSC cocultured, and 5) anti-p75 antibody-treated OLGs. After an additional 3 hr of reoxygenation incubation, OLG viability and apoptosis were measured. The mRNA expression in the BMSCs and OLGs was analyzed using quantitative real-time PCR (RT-PCR). Serine/threonine-specific protein kinase (Akt), phosphorylated Akt (p-Akt), p75, and caspase 3 protein expressions in OLGs were measured by Western blot. Our results suggest that BMSCs produce growth factors, activate the Akt pathway, and increase the survival of OLGs. BMSCs also reduce p75 and caspase 3 expressions in the OGD-OLGs, which leads to decreased OLG apoptosis. BMSCs participate in OLG protection that may occur with promoting growth factors/PI3K/Akt and inhibiting the p75/caspase pathways. Our study provides insight into white matter damage and the therapeutic benefits of BMSC-based remyelinating therapy after stroke and demyelinating diseases. (c) 2008 Wiley-Liss, Inc.

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