

# Henry Ford Health System Publication List August 2008

This is a bibliography of journal articles published by Henry Ford Health System personnel. A search was compiled in PubMed during the month of August 2008, and then imported into EndNote for formatting.

Please [contact us](#) if you would like to receive this publication list via email. If the full-text of the article is not available, you can request it from the Sladen Library by clicking on the [Article Request Form](#) or calling us at (313) 916-2550.

You can access this page at <http://www.henryfordconnect.com/sladen.cfm?id=436>

## Cardiology

Cavalcante, J. L., M. Al-Mallah, et al. (2008). "The relationship between spontaneous echocontrast, transesophageal echocardiographic parameters, and blood hemoglobin levels." *J Am Soc Echocardiogr* **21**(7): 868-72. [PDF Full-Text](#)

Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan 48202, USA.

**BACKGROUND:** Spontaneous echocontrast (SEC) or "smoke" is an intracavitary echocardiographic finding seen in situations of stasis or low blood flow. Increased hematocrit and fibrinogen levels have been associated with SEC in prior studies. Whether low hemoglobin (Hb) levels are an independent predictor of lower prevalence of SEC is a question that remains unanswered. **METHODS:** A total of 266 transesophageal echocardiographic (TEE) studies were reviewed. Hb levels within 1 month from the TEE study were used as the baseline Hb before the study (75% had Hb on the same day of the TEE study). Clinical characteristics and demographics, and all relevant TEE variables including left atrial (LA) size, LA appendage emptying velocity (LAAEV), and presence or absence of SEC, were obtained using electronic patient information system search of TEE reports. Multivariate regression analysis was performed to identify the independent predictors of SEC. **RESULTS:** Two groups were analyzed SEC (n = 45) or no SEC (n = 221). Only 7 patients had both LA and right atrial SEC. On univariate analysis, male sex, greater age, prior coronary artery bypass grafting, low ejection fraction (<50%), atrial fibrillation, renal failure, aortic atheroma, dilated LA, and decreased LAAEV (<40 cm/s) predicted SEC whereas low Hb levels were significantly associated with a lower prevalence of SEC (P = .01). However, after adjusting for clinical and echocardiographic variables, low Hb levels did not independently predict absence of SEC. Low LAAEV (P < .001), dilated LA (P = .001), and prior statin therapy (P = .001) were the most powerful independent predictors of SEC. **CONCLUSION:** A low Hb level is not associated with a lower prevalence of SEC when controlled for clinical and echocardiographic variables. Our study confirms the importance of LAAEV and dilated LA in determining presence of SEC, but also raises interesting questions of the relationship between statins and SEC that warrant further study.

...

## Cardiology

Guerrero, M., K. Athota, et al. (2008). "Vascular endothelial growth factor-165 gene therapy promotes cardiomyogenesis in reperfused myocardial infarction." *J Interv Cardiol* **21**(3): 242-51. [PDF Full-Text](#)

Division of Cardiology, William Beaumont Hospital, Royal Oak, Michigan, USA.  
[mguerre1@hfhs.org](mailto:mguerre1@hfhs.org)

**BACKGROUND:** Vascular endothelial growth factor (VEGF)-165 promotes cardiomyogenesis in chronic myocardial ischemia and nonreperfused myocardial infarction (MI). It is unknown whether this effect is present in reperfused MI. We sought to investigate the effect of VEGF-165 gene therapy on cardiomyogenesis after reperfused MI. **METHODS AND RESULTS:** Twenty-

2799 W Grand Blvd, K-17  
Detroit, MI 48202  
[henryfordconnect.com/sladen](http://henryfordconnect.com/sladen)  
[sladen@sladen.hfhs.org](mailto:sladen@sladen.hfhs.org)  
313 916-2550 voice  
313 874-4730 fax

Hours  
8:30am-7:30pm M-Th  
8:30am-5:00pm F

four Yucatan minipigs underwent thoracotomy and a vascular clamp was placed in the left circumflex artery. Reperfusion was reestablished after 90 minutes, and VEGF-165 gene therapy or placebo was administered. A replication-deficient recombinant human adenovirus serotype 5 was used for gene transfer (Ad5-VEGF165). The same viral vector devoid of VEGF gene (Ad5-beta-galactosidase) was used as placebo. Two administration routes were tested, intramyocardial (IM) injection and circumflex intracoronary (IC) infusion. The pigs were assigned to one of the following groups: IM Ad5-VEGF165 (n = 6), IM Ad5-betaGal (n = 6), IC Ad5-VEGF165 (n = 6), and IC Ad5-betaGal (n = 6). All pigs received 5-bromo-2'-deoxyuridine (BrdU) 250 mg IV twice a week to label cells undergoing DNA replication. The hearts were explanted at 4 weeks. BrdU-labeled cardiomyocytes in the peri-infarct area were counted by a pathologist blinded to group assignment. The number of BrdU-labeled cardiomyocytes per million cells was 4-fold higher in the group receiving IM VEGF-165 (64 +/- 11.4) vs. IM placebo (16 +/- 10.6), P = 0.034. No difference in infarct size or ventricular function was observed between the groups. CONCLUSIONS: IM VEGF-165 gene therapy promotes cardiomyogenesis in reperfused MI. However, no benefit in infarct size or cardiac function was observed at 4 weeks. The origin of these cells remains unknown and needs to be determined.

...

### Cardiology

Jaffery, Z. and K. Ananthasubramaniam (2008). "A rare side effect of transesophageal echocardiography: methemoglobinemia from topical benzocaine anesthesia." *Eur J Echocardiogr* **9**(2): 289-90. [Article Request Form](#)

Department of Internal Medicine, Heart and Vascular Institute, Henry Ford Hospital, 2799 West Grand Boulevard, K-14, Detroit, MI 48202, USA.

BACKGROUND: Benzocaine induced methemoglobinemia is an uncommon, potentially fatal condition. CASE REPORT: A 44-year-old woman with a history of hepatitis C and intravenous drug use was referred for transesophageal echocardiography for bacteremia evaluation. During induction of topical anesthesia with benzocaine spray she became cyanotic. Pulse oximetry revealed marked desaturation (75%) but was discordant from arterial blood O<sub>2</sub> saturation (99%). Due to clinical suspicion, methemoglobin level was measured and noted to be 69%. The patient was treated with 2 mg/kg of methylene blue intravenously with resolution of her symptoms. CONCLUSION: Physicians using topical anesthesia in endoscopic suites should be aware of this rare, potentially life-threatening treatable condition. High clinical suspicion and availability of methylene blue in endoscopy suites will facilitate prompt diagnosis and treatment.

...

### Cardiology

Jennings, D. L. and J. S. Kalus (2008). "Focus on...Tolvaptan." *Formulary*. **43**(7): 236-8, 240-1, 248, 249. [PDF Full-Text](#)

Cardiovascular Specialty Resident, Henry Ford Hospital, Detroit, MI.

...

### Cardiology

Keteyian, S. J., C. A. Brawner, et al. (2008). "Peak aerobic capacity predicts prognosis in patients with coronary heart disease." *Am Heart J* **156**(2): 292-300. [PDF Full-Text](#)

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI, USA. [sketeyi1@hfhs.org](mailto:sketeyi1@hfhs.org)

BACKGROUND: It is unknown if contemporary preventive treatments such as statins or primary percutaneous coronary intervention in patients with coronary heart disease (CHD) have rendered obsolete the use of measured exercise capacity for assessment of future risk and prognosis. Using a sample of patients from 2 clinical sites, most of whom were taking beta-blockade, antiplatelet, and statin therapy, we hypothesized that peak oxygen consumption (Vo<sub>2</sub>) would remain a strong and independent predictor of all-cause and cardiovascular-specific mortality in men and women with CHD. METHODS: We studied 2,812 patients with CHD between 1996 and 2004. All-cause and cardiovascular disease-specific mortality served as end points. RESULTS: In all men and women and in a subgroup of patients following evidence-based care, peak Vo<sub>2</sub> remained a strong predictor of all-cause death, with every 1 mL x kg<sup>-1</sup> x min<sup>-1</sup> increase in peak Vo<sub>2</sub> associated with

an approximate 15% decrease in risk of death. Among men, a peak  $Vo(2)$  ( $mL \times kg^{-1} \times min^{-1}$ ) below approximately 15 was associated with the highest risk, whereas a peak  $Vo(2)$  above approximately 19 was associated with a low rate and risk for annual all-cause mortality. Among women, a peak  $Vo(2)$  below approximately 12 was associated with the highest risk, whereas a peak  $Vo(2)$  above approximately 16.5 was associated with the lowest rate and risk for annual all-cause mortality. CONCLUSIONS: In men and women with CHD, peak  $Vo(2)$  remains an independent predictor of all-cause and cardiovascular-specific mortality.

...

### **Diagnostic Radiology**

Pawelczyk, E., A. S. Arbab, et al. (2008). "In vitro model of bromodeoxyuridine or iron oxide nanoparticle uptake by activated macrophages from labeled stem cells: implications for cellular therapy." *Stem Cells* **26**(5): 1366-75.

[Article Request Form](#)

Experimental Neuroimaging Section, Laboratory of Diagnostic Radiology Research, Clinical Center, Henry Ford Health System, Detroit, Michigan, USA. [pawelczyk@cc.nih.gov](mailto:pawelczyk@cc.nih.gov)

There is increasing interest in using exogenous labels such as bromodeoxyuridine (BrdU) or superparamagnetic iron oxide nanoparticles (SPION) to label cells to identify transplanted cells and monitor their migration by fluorescent microscopy or in vivo magnetic resonance imaging (MRI), respectively. Direct implantation of cells into target tissue can result in >80% cell death due to trauma or apoptosis. Bystander uptake of labeled cells by activated macrophages (AM) can confound the interpretation of results. This study investigated the frequency of BrdU or SPION uptake by AM using the Boyden chamber model of inflammation. SPION/BrdU-labeled bone marrow stromal cells or HeLa cells, AM, and mouse fibroblasts (MF) or human fibroblasts (HF) were mixed in various ratios in Matrigel in the upper chamber and incubated for up to 96 hours. The AM were chemotactically induced to migrate to the lower chamber. Fluorescence-activated cell sorting analysis of AM from lower and upper chambers, in the presence of either MF or HF using anti-CD68, anti-BrdU, anti-dextran antibodies, revealed 10%-20% dextran-positive or 10% BrdU-positive AM after 96 hours of incubation. Transfer of iron to AM accounted for <10% of the total iron in labeled cells. The uptake of BrdU and SPION was dependent on the ratio of labeled cells to inflammatory cells and microenvironmental conditions. Direct implantation of BrdU/SPION-labeled cells into target tissue can result in uptake of label by AM; therefore, care should be taken to validate by histology transplanted cells for bystander cell markers and correlation with MRI results.

...

### **Diagnostic Radiology**

Price, M. C. and E. M. Negussie (2008). "True embryologic ectopic ovary." *Applied Radiology*. **37**(5): 14-15.

[Article Request Form](#)

Henry Ford Hospital. Detroit, MI.

...

### **Diagnostic Radiology**

Soltanian-Zadeh, H., H. Bagher-Ebadian, et al. (2007). "Multiparametric iterative self-organizing data analysis of ischemic lesions using pre- or post-Gd T1 MRI." *Cerebrovasc Dis* **23**(2-3): 91-102. [Article Request Form](#)

Image Analysis Laboratory, Department of Radiology, Henry Ford Health System, Detroit, MI 48202, USA.

[hamids@rad.hfh.edu](mailto:hamids@rad.hfh.edu)

BACKGROUND: The purpose of this work was to evaluate effects of Gd-diethylenetriaminepentaacetic acid (DTPA) injection on T(1)-weighted images of stroke and lesion segmentation and characterization results generated by our multiparametric iterative self-organizing data (ISODATA) method. The post-Gd image incorporates vasculature information into the analysis. METHODS: Either a pre-Gd T(1)-weighted image (T1WI) or a post-Gd T1WI was used along with diffusion-, T(2)- and proton-density-weighted images in the analysis. ISODATA is a data-driven method that segments and characterizes tissue damage in stroke using multiparametric MRI. RESULTS: Experimental results in both animal and human studies showed that the use of post-Gd T1WI modified the segmentation and characterization results on the periphery of the lesion. The peripheral

region that changes with Gd-DTPA has a higher permeability compared to the rest of the lesion. Either of the data sets (including pre- or post-Gd T1WI) was used to estimate the tissue recovery and generated consistent results. CONCLUSIONS: This study shows that our multiparametric ISODATA approach consistently identifies and characterizes the core of the ischemic lesion. It also shows that the inclusion of post-Gd T1WI results in the segmentation and characterization of the lesion periphery if it has a higher permeability compared to the rest of the lesion. Finally, it confirms that the multiparametric ISODATA MRI characterizes tissue damage and recovery in stroke.

...

### **Emergency Medicine**

Lewandowski, C. A., C. P. Rao, et al. (2008). "Transient ischemic attack: definitions and clinical presentations." *Ann Emerg Med* **52**(2): S7-16. [PDF Full-Text](#)

Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, USA.

The definition of transient ischemic attack has changed from a focal, neurologic event that lasts less than 24 hours to one that typically lasts less than 1 hour and is not associated with changes on neuroimaging. Transient ischemic attacks, using the older definition, carry a 10% risk of stroke within 90 days and are therefore considered a serious condition meriting urgent attention. The manifestations of transient ischemic attacks are varied and include events that involve the anterior and posterior cerebral circulations. Correct diagnosis depends on an accurate medical history and physical examination, combined with the appropriate neuroimaging. It is uncommon that syndromes such as syncope, isolated dizziness, drop attacks, or global amnesia are caused by cerebral ischemia or transient ischemic attack. With the careful evaluation of symptoms according to this definition of transient ischemic attack, a clinician can determine whether a transient ischemic attack has occurred and thus propose treatment that may decrease the likelihood of a subsequent stroke.

...

### **Gastroenterology**

Antaki, F., M. M. French, et al. (2008). "Bioelectrical impedance analysis for the evaluation of hepatic fibrosis in patients with chronic hepatitis C infection." *Dig Dis Sci* **53**(7): 1957-60. [PDF Full-Text](#)

Division of Gastroenterology, John D. Dingell VA Medical Center, 4646 John R Road, Detroit, MI 48201, USA.

Bioelectrical impedance analysis (BIA) is a non-invasive technique that measures electrical resistance (R) and reactance (Xc), which are then used to calculate phase angle (PA). The aim of this pilot study was to assess whether BIA can differentiate between minimal and advanced hepatic fibrosis in patients with chronic hepatitis C (HCV) infection. Twenty patients with HCV participated in this study, and were divided into minimal (Metavir 1) and advanced (Metavir 3 or 4) fibrosis groups. We obtained BIA measurements (R and Xc) in several axes and calculated PA from each pair of measurements. We found no statistically significant differences between the two groups with respect to PA, R, or Xc for the whole body, the trunk or the right upper quadrant measurements in any axis. Mean whole body PA was 7.0 and 7.1 (P = 0.9) in the minimal and advanced fibrosis groups, respectively. Bioelectrical impedance analysis did not demonstrate the ability to distinguish between minimal and advanced degrees of hepatic fibrosis in patients with chronic HCV infection.

...

### **Gastroenterology**

McHutchison, J. G., B. R. Bacon, et al. (2007). "Phase 1B, randomized, double-blind, dose-escalation trial of CPG 10101 in patients with chronic hepatitis C virus." *Hepatology* **46**(5): 1341-9. [PDF Full-Text](#)

ALT (Alliance for Liver Therapy) Group, Division of Gastroenterology & Hepatology and Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA. [mchut001@mc.duke.edu](mailto:mchut001@mc.duke.edu)

CPG 10101, a synthetic oligodeoxynucleotide (ODN), is a toll-like receptor 9 (TLR9) agonist with antiviral and immunomodulatory properties that could potentially influence chronic infection with HCV. In this multicenter Phase 1b trial, 60 HCV-positive patients (50 genotype 1 HCV) were randomized and received either placebo or CPG 10101 at 0.25, 1, 4, 10, or 20 mg subcutaneously (SC) twice weekly for 4 weeks or at 0.5 or 0.75 mg/kg SC once weekly for 4 weeks. Dose-

dependent cytokine induction was observed after administration of CPG 10101. At 24 hours after administering the highest dose of 0.75 mg/kg CPG 10101, interferon (IFN)-gamma-inducible protein 10 (IP-10) had a mean increase over baseline levels (+/-SD) of 15,057 (+/-9769) pg/ml (P < 0.01, compared to placebo); IFN-alpha had a 106 (+/-63.3) pg/ml increase (P < 0.01); and 2'5'-oligoadenylate synthetase (OAS) had a 163 (+/-120.6) pmol/dl increase (P < 0.01). Decreases in HCV RNA also were dose-dependent, with the greatest group geometric mean maximum reduction of 1.69 +/- 0.618 log(10) (P < 0.05) observed in the 0.75 mg/kg dose group. Decreases >=1 log(10) were seen in 22 of 40 patients who received >=1 mg CPG 10101, with 3 patients exceeding a 2.5-log(10) reduction. CPG 10101 was well tolerated, and adverse events were consistent with CPG 10101's mechanism of action. Conclusion: In this Phase 1 study, CPG 10101 was associated with dose-dependent increases in markers of immune activation and decreases in HCV RNA levels. The data support further clinical studies of CPG 10101 for treating chronic HCV infection.

...

## Gastroenterology

McHutchison, J. G., G. Dusheiko, et al. (2007). "Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C." *N Engl J Med* **357**(22): 2227-36. [PDF Full-Text](#)

Duke University and Duke Clinical Research Institute, Durham, NC 27705, USA. [mchut001@mc.duke.edu](mailto:mchut001@mc.duke.edu)

BACKGROUND: Eltrombopag is a new, orally active thrombopoietin-receptor agonist that stimulates thrombopoiesis. We evaluated its ability to increase platelet counts and facilitate treatment for hepatitis C virus (HCV) infection in patients with thrombocytopenia associated with HCV-related cirrhosis. METHODS: Seventy-four patients with HCV-related cirrhosis and platelet counts of 20,000 to less than 70,000 per cubic millimeter were randomly assigned to receive eltrombopag (30, 50, or 75 mg daily) or placebo daily for 4 weeks. The primary end point was a platelet count of 100,000 per cubic millimeter or more at week 4. Peginterferon and ribavirin could then be initiated, with continuation of eltrombopag or placebo for 12 additional weeks. RESULTS: At week 4, platelet counts were increased to 100,000 per cubic millimeter or more in a dose-dependent manner among patients for whom these data were available: in 0 of the 17 patients receiving placebo, in 9 of 12 (75%) receiving 30 mg of eltrombopag, in 15 of 19 (79%) receiving 50 mg of eltrombopag, and in 20 of 21 (95%) receiving 75 mg of eltrombopag (P<0.001). Antiviral therapy was initiated in 49 patients (in 4 of 18 patients receiving placebo, 10 of 14 receiving 30 mg of eltrombopag, 14 of 19 receiving 50 mg of eltrombopag, and 21 of 23 receiving 75 mg of eltrombopag) while the administration of eltrombopag or placebo was continued. Twelve weeks of antiviral therapy, with concurrent receipt of eltrombopag or placebo, were completed by 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively, and by 6% of patients in the placebo group. The most common adverse event during the initial 4 weeks was headache; thereafter, the adverse events were those expected with interferon-based therapy. CONCLUSIONS: Eltrombopag therapy increases platelet counts in patients with thrombocytopenia due to HCV-related cirrhosis, thereby permitting the initiation of antiviral therapy. (ClinicalTrials.gov number, NCT00110799.)

...

## Gastroenterology

Moonka, D., K. A. Milkovich, et al. (2008). "Hepatitis C specific T cell IFN- $\gamma$  and proliferative responses are more common in perihepatic lymph nodes than in peripheral blood or liver." *J Virol*. Epub Ahead of Print. [Article Request Form](#)

Division of Gastroenterology, Transplant Surgery, Henry Ford Health System, Detroit Michigan; Department of Medicine, Divisions of Infectious and Rheumatic Diseases, Case Western Reserve University, University Hospitals of Cleveland, Center for AIDS Research and VA Medical Center, Cleveland OH.

The activation state, differentiation state and function of liver lymphocytes and perihepatic lymph nodes during chronic hepatitis C virus (HCV) infection are not well understood. Here we performed phenotypic and functional analysis of freshly prepared lymphocytes isolated from liver, perihepatic lymph nodes, and peripheral blood compartments of chronic HCV infected and disease control subjects with end-stage liver disease undergoing liver transplantation. We measured lymphocyte subset frequency, and memory T cell IFN-gamma and proliferative responses to HCV peptide and control viral antigens in direct ex vivo assays. We found greater frequencies of CD4 cells in the lymph node compartment for both HCV infected and disease control subjects. Lymph node CD4 and CD8 cells less commonly expressed the terminal differentiation marker CD57, consistent with an earlier differentiation state. In HCV infected subjects, HCV specific IFN-gamma producing

and proliferative responses were commonly observed in the lymph node fraction, while they were uncommonly observed in the peripheral blood or liver fractions. In contrast, control viral CD4 protein antigen and CD8 peptide antigen specific IFN-gamma responses were commonly observed in the periphery, and uncommonly observed in the lymph node of these same subjects. These findings are consistent with a selective defect in HCV specific T cell effector function or distribution in patients with advanced chronic HCV infection. The high frequency of HCV reactive T cells in perihepatic lymph nodes indicates that a failure to generate or sustain T lymphocyte HCV reactivity is not responsible for the paucity of functional cells even in end-stage liver disease.

...

### **Hematology, Medical Oncology & Josephine Ford Cancer Center**

Dabak, V., P. Kuriakose, et al. (2008). "A pilot study of thalidomide in recurrent GI bleeding due to angiodysplasias." *Dig Dis Sci* **53**(6): 1632-5. [PDF Full-Text](#)

Josephine Ford Cancer Center, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA. [vdabak1@hfhs.org](mailto:vdabak1@hfhs.org)

Angiodysplasias are a major cause of lower gastrointestinal bleeding in patients over the age of 60 years. Although multiple treatment modalities, both medical and surgical, are being used, there is no effective treatment option currently available. Our study defines the use of a novel drug that might be effective against bleeding from vascular malformations. Three patients with a diagnosis of angiodysplasia, who were transfusion dependent, were placed on the study drug. The need for blood transfusions was recorded over the study period and for 6 months after the end of the study. We saw a decreased need for transfusions within 12 weeks of starting the treatment in two patients, and they continued to remain free of transfusion requirement during the immediate follow-up period. The study drug was well tolerated. Thalidomide, with its antiangiogenic mechanism of action, seems to be a promising drug in bleeding angiodysplasias as a treatment option for patients unable to benefit from other available modalities of treatment.

...

### **Hypertension and Vascular Research**

Ardanaz, N., W. H. Beierwaltes, et al. (2007). "Comparison of H<sub>2</sub>O<sub>2</sub>-induced vasoconstriction in the abdominal aorta and mesenteric artery of the mouse." *Vascul Pharmacol* **47**(5-6): 288-94. [Article Request Form](#)

Hypertension and Vascular Research Division, Henry Ford Health System, Detroit, MI 48202-2689, USA.

Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is generally perceived as an arterial vasodilator. Due to the emerging importance of H<sub>2</sub>O<sub>2</sub> as a possible vasoconstrictor, we examined whether H<sub>2</sub>O<sub>2</sub> constricts both the abdominal aorta and superior mesenteric artery and postulated that H<sub>2</sub>O<sub>2</sub> is a ubiquitous constrictor of quiescent mouse arteries. Moreover, we postulated that KCl depolarization discloses and/or exaggerates H<sub>2</sub>O<sub>2</sub>-induced constriction. Under quiescent conditions, H<sub>2</sub>O<sub>2</sub> constricted the mouse abdominal aorta but not the mesenteric artery. Vessel depolarization (a) exaggerated this constrictor response in the aorta, and (b) unmasked a contractile response in the mesenteric artery. Our final hypothesis tested whether tyrosine kinases, mitogen-activated protein kinases (MAPKs), and/or Rho-kinase are uniformly involved in H<sub>2</sub>O<sub>2</sub>-induced vasoconstriction. We observed a marked difference in the ability of tyrosine kinase inhibitor to block H<sub>2</sub>O<sub>2</sub>-induced vasoconstriction. p38 and ERK 1/2MAPK inhibitors reduced the maximal response to H<sub>2</sub>O<sub>2</sub>, whereas JNK inhibitor had no effect. Finally, Rho-kinase inhibitor decreased the H<sub>2</sub>O<sub>2</sub> response in the mesenteric artery but not in the aorta. These data demonstrate a variable yet tightly regulated H<sub>2</sub>O<sub>2</sub> vasoconstrictor effect. Furthermore, we found that p38, ERK 1/2 and Rho-kinase play a role in H<sub>2</sub>O<sub>2</sub> constriction, which may be critical pathways involved in H<sub>2</sub>O<sub>2</sub>-induced constriction across vascular beds.

...

### **Hypertension and Vascular Research**

Ares, G. R., P. S. Caceres, et al. (2008). "cGMP decreases surface NKCC2 levels in the thick ascending limb: role of phosphodiesterase 2 (PDE2)." *Am J Physiol Renal Physiol*. Epub Ahead of Print. [PDF Full-Text](#)

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

NaCl absorption in the medullary thick ascending limb (THAL) is mediated by the apical Na/K/2Cl cotransporter (NKCC2). Hormones that increase cGMP such as NO and natriuretic peptides decrease NaCl absorption by the THAL. However, the mechanism by which cGMP decreases NaCl absorption in THALs is unknown. We hypothesized that cGMP decreases surface NKCC2 levels in the THAL. We used surface biotinylation to measure surface NKCC2 levels in rat mTHAL suspensions. We first tested the effect of the membrane-permeant cGMP analogue dibutyryl-cGMP. Incubating THALs with db-cGMP for 20 min decreased surface NKCC2 levels in a concentration-dependent manner (basal = 100 %; db-cGMP 100µM = 77 +/-7 %; 500µM = 54 +/-10 % and 1000µM = 61 +/-8 %). A different cGMP analogue (8-Br-cGMP) also decreased surface NKCC2 levels by 25 %, (basal = 100 %; 8-Br-cGMP = 75 +/-5 %). Incubation of perfused THALs with db-cGMP decreased apical surface NKCC2 labeling as measured by immunofluorescence and confocal microscopy. cGMP-stimulated phosphodiesterase 2 (PDE2) mediates the effect of NO on NaCl absorption. Thus we examined the role of PDE2 and found that PDE2 inhibitors blocked the effect of db-cGMP on surface NKCC2. Also, a non-stimulatory concentration of db-cAMP blocked cGMP's effect. Finally, db-cGMP inhibited THAL net Cl absorption by 48 +/- 4%, and this effect was abolished by PDE2 inhibition. We concluded that cGMP decreases NKCC2 in the apical membrane of THALs and this effect is mediated by PDE2. This is an important mechanism by which cGMP inhibits NaCl absorption by the THAL. Key words: Na/K/2Cl cotransport, trafficking, nitric oxide, PDE2a, apical.

...

### **Hypertension and Vascular Research**

Liao, T. D., X. P. Yang, et al. (2008). "Role of inflammation in the development of renal damage and dysfunction in angiotensin II-induced hypertension." *Hypertension* **52**(2): 256-63. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Henry Ford Hospital, 2799 West Grand Blvd, Detroit MI 48202-2689, USA.

Angiotensin II (Ang II)-induced hypertension is associated with an inflammatory response that may contribute to the development of target organ damage. We tested the hypothesis that, in Ang II-induced hypertension, CC chemokine receptor 2 (CCR2) activation plays an important role in the development of renal fibrosis, damage, and dysfunction by causing oxidative stress, macrophage infiltration, and cell proliferation. To test this hypothesis, we used CCR2 knockout mice (CCR2<sup>-/-</sup>). The natural ligand of CCR2 is monocyte chemoattractant protein-1, a chemokine important for macrophage recruitment and activation. CCR2<sup>-/-</sup> and age-matched wild-type (CCR2<sup>+/+</sup>) C57BL/6J mice were infused continuously with either Ang II (5.2 ng/10 g per minute) or vehicle via osmotic minipumps for 2 or 4 weeks. Ang II infusion caused similar increases in systolic blood pressure and left ventricular hypertrophy in both strains of mice. However, in CCR2<sup>-/-</sup> mice with Ang II-induced hypertension, oxidative stress, macrophage infiltration, albuminuria, and renal damage were significantly decreased, and glomerular filtration rate was significantly higher than in CCR2<sup>+/+</sup> mice. We concluded that, in Ang II-induced hypertension, CCR2 activation plays an important role in the development of hypertensive nephropathy via increased oxidative stress and inflammation.

...

### **Hypertension and Vascular Research**

Ren, Y., M. A. D'Ambrosio, et al. (2008). "Heme oxygenase metabolites inhibit tubuloglomerular feedback (TGF)." *Am J Physiol Renal Physiol*. Epub Ahead of Print. [PDF Full-Text](#)

Henry Ford Hospital.

Tubuloglomerular feedback (TGF) is the mechanism by which the macula densa (MD) senses increases in luminal NaCl concentration and sends a signal to constrict the afferent arteriole (Af-Art). The kidney expresses constitutively heme oxygenase-2 (HO-2), and low levels of HO-1. HOs release carbon monoxide (CO), biliverdin and free iron. We hypothesized that renal HOs inhibit TGF via release of CO and biliverdin. Rabbit Af-Arts and attached MD were simultaneously microperfused in vitro. TGF response was determined by measuring Af-Art diameter before and after increasing NaCl in the MD perfusate. When HO activity was inhibited by adding stannous mesoporphyrin (SnMP) to the MD perfusate, TGF response increased from 2.1 +/- 0.2 microm to 4.1 +/- 0.4 microm (p = 0.003, control vs SnMP, n = 7). When a CO-releasing

molecule, CORM-3 (50 microM) was added to the MD perfusate, TGF response decreased by 41%, from 3.6+/-0.3 microm to 2.1+/-0.2 microm ( $p < 0.001$ , control vs CORM-3,  $n = 12$ ). When CORM-3 at 100 microM was added to the perfusate, it completely blocked TGF response, from 4.2+/-0.4 microm to -0.2+/-0.3 microm ( $p < 0.001$ , control vs CORM-3,  $n = 6$ ). When biliverdin was added to the perfusate, TGF response decreased by 79%, from 3.4+/-0.3 microm to 0.7+/-0.4 microm ( $p = 0.001$ , control vs biliverdin,  $n = 6$ ). The effects of SnMP and CORM-3 were not blocked by inhibition of nitric oxide synthase. We concluded that renal HO inhibits TGF probably via release of CO and biliverdin. HO regulation of TGF is a novel mechanism that could lead to a better understanding of the control of renal microcirculation and function. Key words: carbon monoxide, biliverdin, afferent arteriole, Tubuloglomerular feedback.

...

## Hypertension and Vascular Research

Silva, G. B. and J. L. Garvin (2008). "TRPV4 mediates hypotonicity-induced ATP release by the thick ascending limb." *Am J Physiol Renal Physiol*. Epub Ahead of Print. [PDF Full-Text](#)

Henry Ford Hospital.

Extracellular ATP is an autocrine/paracrine factor that regulates renal function. TRPV4 is a cation channel that mediates release of autocrine/paracrine factors by acting as an osmosensor. The renal medulla, and therefore the thick ascending limb, is exposed to osmotic stress. We hypothesize that reduced osmolality stimulates ATP release from the thick ascending limb via TRPV4 activation. We measured ATP release by medullary thick ascending limb suspensions after reducing bath osmolality from 350 to 323 mOsm/KgH<sub>2</sub>O, using the luciferin-luciferase assay. Decreasing osmolality stimulated ATP release compared to control (38.9+/-7.2 vs. 2.4+/-1.0 pmol/mg protein;  $n=6$ ,  $p<0.01$ ). To examine the role of TRPV4, we used 1) Ca-free solutions 2) a TRPV4 inhibitor 3) siRNA against TRPV4 and 4) a TRPV4 activator. Removal of Ca completely blocked osmolality-induced ATP release (42.2+/-5.9 vs. 2.6+/-1.5 pmol/mg protein;  $n=6$ ,  $p<0.01$ ). In the presence of the TRPV4-selective inhibitor ruthenium red, osmolality-induced ATP release was blocked by 73% (56.4+/-19.9 vs. 8.8+/-2.3 pmol/mg protein;  $n=6$ ;  $p<0.03$ ). In vivo treatment of thick ascending limbs with siRNA against TRPV4 decreased osmolality-induced ATP release by 62% (31.5+/-3.4 vs. 12.4+/-1.1 pmol/mg protein;  $n=7$ ;  $p<0.01$ ), while reducing TRPV4 expression by 74% compared to the non-treated kidney. Treatment with scrambled siRNA did not affect TRPV4 expression and/or osmolality-induced ATP release. Finally, in the absence of changes in osmolality, the specific TRPV4 agonist 4alpha-PDD increased ATP release (3.6+/-0.9 vs. 25.4+/-7.4 pmol/mg protein;  $n=6$ ;  $p<0.04$ ). We concluded that decreases in osmolality stimulate ATP release by thick ascending limbs and this effect is mediated by TRPV4 activation. Key words: osmosensor, cell swelling, calcium channels, hyposmolality.

...

## Infectious Diseases

Chua, T., C. L. Moore, et al. (2008). "Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* bloodstream isolates in urban Detroit." *J Clin Microbiol* **46**(7): 2345-52. [Article Request Form](#)

Henry Ford Health System, Wayne State University School of Medicine, Detroit, Michigan 48202, USA.

To gain a better understanding of epidemiology of resistance in *Staphylococcus aureus*, we describe the molecular epidemiology of methicillin-resistant *Staphylococcus aureus* bloodstream isolates in urban Detroit. Bloodstream isolates from July 2005 to February 2007 were characterized. Two hundred ten bloodstream isolates from 201 patients were evaluated. Patient characteristics were as follows: median age, 54 years; 56% male; and 71% African-American. Seventy-six percent of infections were health care associated, with 55% being community-onset infections and 21% hospital acquired, and 24% were community associated. The most common sources were skin/wound (25%), central venous catheters (24%), unknown source (20%), and endocarditis (9%). Ninety percent and 5% of isolates had a MIC of vancomycin of  $\leq 1.0$  mg/liter, using automated dilution testing and E-test, respectively. Six percent of isolates showed heteroresistance to vancomycin, all occurring with isolates having a vancomycin E-test MIC of  $\geq 1.5$  mg/liter. Results of pulsed-field gel electrophoresis showed 17 strain types. The predominant strains were USA100 (104 isolates) and USA300 (74 isolates). Forty-nine percent of the isolates had staphylococcal cassette chromosome mec II, and 56% had agr II. All USA300 isolates were positive for the Pantone-Valentine leukocidin toxin genes and agr I. Forty-seven percent of USA300 bloodstream infections were health care associated (35% community onset and 12% hospital onset). USA300 strains were more common in injection drug users with skin/wound as the predominant source of infection. Thirty percent of the USA100 strains were closely related to vancomycin-resistant *Staphylococcus aureus* isolates. The results of this study show that vancomycin MICs

using automated dilution testing with Vitek-2 and E-test were highly discordant. Most methicillin-resistant *S. aureus* strains causing bacteremia are health care associated, commonly have MICs of vancomycin that are high within the susceptible range are not detected by routine automated dilution testing, and have significant diversity of molecular characteristics. USA100 strains that are closely related to vancomycin-resistant *S. aureus* (VRSA) isolates and USA300 strains are common as causes of both hospital and community-onset infection. Infection control measures should focus not only on prevention of the spread of community strains in the hospital but also prevention of the spread of hospital strains associated with VRSA into the community.

...

### Internal Medicine

Aichbaumik, N., E. M. Zoratti, et al. (2008). "Prenatal exposure to household pets influences fetal immunoglobulin E production." *Clin Exp Allergy*. Epub Ahead of Print. [PDF Full-Text](#)

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

**Background** Early life pet exposure may protect against allergic sensitization during childhood. Few studies have evaluated the effect of prenatal pet exposure on potential neonatal markers of allergic risk. **Objective** The aim of this study was to investigate whether maternal exposure to pets affects cord blood IgE levels in a population-based, general risk, ethnically mixed birth cohort. **Methods** Pet keeping during pregnancy was ascertained from women residing in a defined area of Wayne County Michigan and recruited from five staff model obstetric clinics. Maternal venous blood was analysed for total and allergen-specific IgE along with cord blood total IgE from 1049 infants. **Results** Compared with infants from households with no cats or dogs kept indoors during pregnancy, infants whose homes had either cats or dogs had significantly reduced mean cord IgE levels [0.34 IU/mL (95% CI 0.30-0.38) vs. 0.24 IU/mL (0.20-0.27),  $P=0.025$ ]. Similar effects were apparent in cat-only households [0.21 IU/mL (0.16-0.27),  $P=0.020$ ] and dog-only households [0.24 IU/mL (0.19-0.29),  $P=0.045$ ]. There was no effect on results when excluding mothers who reported avoiding pets due to allergy-related concerns. **Conclusion** Mothers with either cats or dogs in their home during pregnancy deliver children with lower cord blood IgE levels compared with mothers who do not live with these pets, supporting the hypothesis that pet exposure influences immune development in a manner that is protective for atopy and is operant even before birth.

...

### Internal Medicine

Shiffman, M. L., F. Suter, et al. (2007). "Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3." *N Engl J Med* **357**(2): 124-34. [PDF Full-Text](#)

Virginia Commonwealth University Medical Center, Richmond, VA 23298, USA. [mshiffma@vcu.edu](mailto:mshiffma@vcu.edu)

**BACKGROUND:** Patients infected with hepatitis C virus (HCV) genotype 2 or 3 have sustained virologic response rates of approximately 80% after receiving treatment with peginterferon and ribavirin for 24 weeks. We conducted a large, randomized, multinational, noninferiority trial to determine whether similar efficacy could be achieved with only 16 weeks of treatment with peginterferon alfa-2a and ribavirin. **METHODS:** We randomly assigned 1469 patients with HCV genotype 2 or 3 to receive 180 mug of peginterferon alfa-2a weekly, plus 800 mg of ribavirin daily, for either 16 or 24 weeks. A sustained virologic response was defined as an undetectable serum HCV RNA level (<50 IU per milliliter) 24 weeks after the end of treatment. **RESULTS:** The study failed to demonstrate that the 16-week regimen was noninferior to the 24-week regimen. The sustained virologic response rate was significantly lower in patients treated for 16 weeks than in patients treated for 24 weeks (62% vs. 70%; odds ratio for 16 weeks vs. 24 weeks, 0.67; 95% confidence interval, 0.54 to 0.84;  $P<0.001$ ). In addition, the rate of relapse (a detectable HCV RNA level during follow-up in patients who had undetectable HCV RNA at the end of treatment) was significantly greater in the 16-week group (31%, vs. 18% in the 24-week group;  $P<0.001$ ). The sustained virologic response rates in patients with a pretreatment serum HCV RNA level of 400,000 IU per milliliter or less was 82% with the 16-week regimen and 81% with the 24-week regimen. Among patients with a rapid virologic response (an undetectable HCV RNA level by week 4), sustained virologic response rates were 79% in the 16-week group and 85% in the 24-week group ( $P=0.02$ ). **CONCLUSIONS:** Treatment with peginterferon and ribavirin for 16 weeks in patients infected with HCV genotype 2 or 3 results in a lower overall sustained virologic response rate than treatment with the standard 24-week regimen. (ClinicalTrials.gov number, NCT00077636 [ClinicalTrials.gov].).

...

## Neurology

Cui, X., J. Chen, et al. (2008). "Treatment of stroke with (Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl) amino] diazen-1-ium-1, 2-diolate and bone marrow stromal cells upregulates angiopoietin-1/Tie2 and enhances neovascularization." Neuroscience. EPub Ahead of Print. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, MI 48202, USA.

Neovascularization may contribute to functional recovery after neural injury. Combination treatment of stroke with a nitric oxide donor, (Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl) amino] diazen-1-ium-1, 2-diolate (DETA-NONOate) and bone marrow stromal cells promotes functional recovery. However, the mechanisms underlying functional improvement have not been elucidated. In this study, we tested the hypothesis that combination treatment upregulates angiopoietin-1 and its receptor Tie2 in the ischemic brain and bone marrow stromal cells, thereby enhancing cerebral neovascularization after stroke. Adult wild type male C57BL/6 mice were i.v. administered PBS, bone marrow stromal cells 5x10<sup>5</sup>, DETA-NONOate 0.4 mg/kg or combination DETA-NONOate with bone marrow stromal cells (n=12/group) after middle cerebral artery occlusion. Combination treatment significantly upregulated angiopoietin-1/Tie2 and tight junction protein (occludin) expression, and increased the number, diameter and perimeter of blood vessels in the ischemic brain compared with vehicle control (mean+/-S.E., P<0.05). In vitro, DETA-NONOate significantly increased angiopoietin-1/Tie2 protein (n=6/group) and Tie2 mRNA (n=3/group) expression in bone marrow stromal cells. DETA-NONOate also significantly increased angiopoietin-1 protein (n=6/group) and mRNA (n=3/group) expression in mouse brain endothelial cells (P<0.05). Angiopoietin-1 mRNA (n=3/group) was significantly increased in mouse brain endothelial cells treated with DETA-NONOate in combination with bone marrow stromal cell-conditioned medium compared with cells treated with bone marrow stromal cell-conditioned medium or DETA-NONOate alone. Mouse brain endothelial cell capillary tube-like formation assays (n=6/group) showed that angiopoietin-1 peptide, the supernatant of bone marrow stromal cells and DETA-NONOate significantly increased capillary tube formation compared with vehicle control. Combination treatment significantly increased capillary tube formation compared with DETA-NONOate treatment alone. Inhibition of angiopoietin-1 significantly attenuated combination treatment-induced tube formation. Our data indicated that combination treatment of stroke with DETA-NONOate and bone marrow stromal cells promotes neovascularization, which is at least partially mediated by upregulation of the angiopoietin-1/Tie2 axis.

...

## Neurology

Cui, X., J. Chen, et al. (2008). "Nitric oxide donor up-regulation of SDF1/CXCR4 and Ang1/Tie2 promotes neuroblast cell migration after stroke." J Neurosci Res. EPub Ahead of Print. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, Michigan.

We tested the hypothesis that a nitric oxide donor, DETA-NONOate, up-regulates stromal cell-derived factor-1 (SDF1) and angiopoietin 1 (Ang1) in the ischemic brain and their respective receptors chemokine CXC motif receptor 4 (CXCR4) and Tie2 in the subventricular zone (SVZ) and thereby promote SVZ neuroblast cell migration after stroke. C57BL/6J mice were subjected to middle cerebral artery occlusion (MCAo), and 24 hr later DETA-NONOate (0.4 mg/kg) or phosphate-buffered solution was intravenously administered. Mice were sacrificed at 14 days for histological assessment or sacrificed at 3 days for analysis by real-time polymerase chain reaction and migration after MCAo. To elucidate whether SDF1/CXCR4 and Ang1/Tie2 pathways mediate DETA-NONOate-induced SVZ migration after stroke, SDF1alpha, Ang1 peptide, a specific antagonist of CXCR4 (AMD3100), and a neutralizing antibody of Tie2 (anti-Tie2) were used in vitro. DETA-NONOate significantly increased the percentage area of doublecortin (DCX, a marker of migrating neuroblasts)-immunoreactive cells in the SVZ and ischemic boundary zone. DETA-NONOate significantly increased the expression of SDF1 and Ang1 in the ischemic border and up-regulated CXCR4 and Tie2 in the SVZ compared with MCAo control. DCX-positive cell migration from SVZ explants was significantly increased in the DETA-NONOate treatment group compared with MCAo-alone animals. In vitro, SDF1alpha and Ang1 significantly increased SVZ explants cell migration. In addition, inhibition of CXCR4 or Tie2 significantly attenuated DETA-NONOate-induced SVZ cell migration. Our data indicate that treatment of stroke with a nitric oxide donor up-regulates SDF1/CXCR4 and Ang1/Tie2 pathways and thereby likely increases SVZ neuroblast cell migration. (c) 2008 Wiley-Liss, Inc.

...

## Neurology

Ding, G., Q. Jiang, et al. (2008). "Magnetic resonance imaging investigation of axonal remodeling and angiogenesis after embolic stroke in sildenafil-treated rats." *J Cereb Blood Flow Metab* **28**(8): 1440-8. [Article Request Form](#)

Department of Neurology, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Interaction between angiogenesis and axonal remodeling after stroke was dynamically investigated by MRI in rats with or without sildenafil treatments. Male Wistar rats were subjected to embolic stroke and treated daily with saline (n=10) or with sildenafil (n=11) initiated at 24 h and subsequently for 7 days after onset of ischemia. T(2)(\*)-weighted imaging, cerebral blood flow (CBF), and diffusion tensor imaging (DTI) measurements were performed from 24 h to 6 weeks after embolization. T(2)(\*) and fractional anisotropy (FA) maps detected angiogenesis and axonal remodeling after stroke, respectively, starting from 1 week in sildenafil-treated rats. Areas demarcated by MRI with enhanced angiogenesis, elevated local CBF, and augmented axonal remodeling were spatially and temporally matched, and FA values were significantly correlated with the corresponding CBF values ( $R=0.66$ ,  $P<4 \times 10^{-5}$ ) at 6 weeks after stroke. Axonal projections were reorganized along the ischemic boundary after stroke. These MRI measurements, confirmed by histology, showed that sildenafil treatment simultaneously enhanced angiogenesis and axonal remodeling, which were MRI detectable starting from 1 week after stroke in rats. The spatial and temporal consistency of MRI metrics and the correlation between FA and local CBF suggest that angiogenesis, by elevating local CBF, promotes axonal remodeling after stroke.

...

## Neurology

Katramados, A. M., D. Burdette, et al. (2008). "Periictal diffusion abnormalities of the thalamus in partial status epilepticus." *Epilepsia*. Epub Ahead of Print. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health Sciences Center, Detroit, Michigan, USA.

Purpose: To identify and describe thalamic dysfunction in patients with temporal as well as extratemporal status epilepticus (SE) and to also analyze the specific clinical, radiological, and electroencephalography (EEG) characteristics of patients with acute thalamic involvement. Methods: We retrospectively identified patients who presented with clinical and electrographic evidence of partial SE and had thalamic abnormalities on diffusion-weighted imaging (DWI) within 5 days of documentation of lateralized epileptiform discharges (group 1). The spatial and temporal characteristics of the periodic lateralized epileptiform discharges (PLEDs) and the recorded electrographic seizures were analyzed and correlated with magnetic resonance imaging (MRI)-DWI hyperintense lesions. The findings of group 1 patients were compared with those of patients with partial SE without thalamic abnormalities on DWI (group 2). Results: The two groups were similar with regard to clinical presentation and morphology of epileptiform discharges. Group 1 patients had thalamic hyperintense lesions on DWI that appeared in the region of the pulvinar nucleus, ipsilateral to the epileptiform activity. Statistically significant relationship was noted between the presence of thalamic lesions and ipsilateral cortical laminar involvement ( $p = 0.039$ ) as well as seizure origin in the posterior quadrants ( $p = 0.038$ ). A trend towards PLEDs originating in the posterior quadrants was also noted ( $p = 0.077$ ). Discussion: Thalamic DWI hyperintense lesions may be observed after prolonged partial SE and are likely the result of excessive activity in thalamic nuclei having reciprocal connections with the involved cortex. The thalamus likely participates in the evolution and propagation of partial seizures in SE.

...

## Neurology

Katramados, A. M., N. Sripathi, et al. (2007). "Intravenous ganciclovir consistently induces remission of persistent Epstein-Barr encephalitis in an HIV-1-infected patient." *Aids* **21**(6): 778-80. [PDF Full-Text](#)

...

## Neurology

Nasrallah, K. M. and P. D. Mitsias (2007). "Orthostatic tremor due to thiamine deficiency." *Mov Disord* **22**(3): 440-1. [PDF Full-Text](#)

...

## Neurology

Schuh, L., D. E. Burdette, et al. (2008). "Learning clinical neurophysiology: gaming is better than lectures." *J Clin Neurophysiol* **25**(3): 167-9. [PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, Detroit, Michigan 48202, USA. [lschuh@neuro.hfh.edu](mailto:lschuh@neuro.hfh.edu)

We sought to find evidence for generalizability of a game and team oriented educational intervention in clinical neurophysiology in a neurology residency program. A prospective educational intervention was studied in a single neurology residency program and compared with a historical control. Seventeen PGY 2-4 residents studied neurophysiology in 2004-2005. The historical control was 20 PGY 2-4 residents from 1998 to 2002. The neurophysiology educational intervention consisted of weekly presentations, followed by a game show-type oral quiz which was team-based and required all residents to participate. The control group attended faculty-prepared didactic lectures. Outcome measures were percent correct subset neurophysiology Residency Inservice Training Examination scores. United States Medical Licensing Examination step 1 scores were also compared between the groups. Data were analyzed with analysis of variance methods accounting for multiple measurements. The mean $\pm$ standard error neurophysiology subset percent correct Residency Inservice Training Examination score was 63.6 $\pm$ 4.12 for the intervention group and 49.4 $\pm$ 2.35 for the control (P=0.002). There was no difference in United States Medical Licensing Examination step 1 scores between the two groups (P=0.11). We found evidence for generalizability of the effectiveness of a team-oriented educational intervention in clinical neurophysiology with gaming and oral quizzing in improving subset Residency Inservice Training Examination performance compared with faculty prepared didactics.

...

## Neurology

Vadikolias, K. M., N. D. Artemis, et al. (2007). "Evaluation of the stability of blood flow over time in the dominant hemisphere: a functional transcranial Doppler study." *J Cereb Blood Flow Metab* **27**(11): 1870-7. [Article Request Form](#)

Department of Neurology, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece. [vadikosm@yahoo.com](mailto:vadikosm@yahoo.com)

Functional transcranial Doppler (fTCD) has been used for the identification of cerebral hemispheric dominance in various cognitive tasks. In our study, we have used fTCD with the aim to compare blood flow patterns in the hemispheres not only during the task activation periods but also in the post-stimulus phase. Normal volunteers, 25 right and 25 left-handed, were included. Mean flow velocities (FVs) in the bilateral middle cerebral arteries were recorded during the performance of six cognitive tasks and during the intervals between tasks. The lateralization index (LI) was calculated separately for each test (LI1-6), on the basis of the percent change of blood FV from baseline. To estimate flow fluctuations, a novel index, the LI-variability, was also calculated using a formula constituted by the minimum and maximum mean values recorded at specific time intervals during the entire procedure. Lateralization indices, LI-3 and LI-4, corresponding to word generation and reading aloud tasks, produced the highest degree of activation. A perfect agreement (Cohen's kappa=1.000, P<0.001) was observed among LI-3, LI-4, and LI-V. The repetition of recordings gave excellent test-retest reliability in 10 randomly selected participants. Our results suggest that the hemisphere that is characterized as dominant by fTCD maintains a more stable flow pattern during the performance of successive cognitive tasks. Although it could not be considered as a clinically useful tool as yet, this observation introduces a novel parameter such as the stability of blood flow over time, which could potentially provide insight in the study of cerebral functions.

...

## Neurology

Wang, L., M. Chopp, et al. (2008). "Neural progenitor cells treated with EPO induce angiogenesis through the production of VEGF." *J Cereb Blood Flow Metab* **28**(7): 1361-8. [Article Request Form](#)

Department of Neurology, Henry Ford Health Sciences Center, Detroit, Michigan 48202, USA.

Recombinant human erythropoietin (rhEPO) induces neurogenesis and angiogenesis. Using a coculture system of mouse brain endothelial cells (MBECs) and neural progenitor cells derived from the subventricular zone of adult mouse, we investigated the hypothesis that neural progenitor cells treated with rhEPO promote angiogenesis. Treatment of neural progenitor cells with rhEPO significantly increased their expression and secretion of vascular endothelial growth factor (VEGF) and activated phosphatidylinositol 3-kinase/Akt (PI3K/Akt) and extracellular signal-regulated kinase (ERK1/2). Selective inhibition of the Akt and ERK1/2 signaling pathways significantly attenuated the rhEPO-induced VEGF expression in neural progenitor cells. The supernatant harvested from neural progenitor cells treated with rhEPO significantly increased the capillary-like tube formation of MBECs. SU1498, a specific VEGF type-2 receptor (VEGFR2) antagonist, abolished the supernatant-enhanced angiogenesis. In addition, coculture of MBECs with neural progenitor cells treated with rhEPO substantially increased VEGFR2 mRNA and protein levels in MBECs. These in vitro results suggest that EPO enhances VEGF secretion in neural progenitor cells through activation of the PI3K/Akt and ERK1/2 signaling pathways and that neural progenitor cells treated with rhEPO upregulate VEGFR2 expression in cerebral endothelial cells, which along with VEGF secreted by neural progenitor cells promotes angiogenesis.

...

## Neurology

Zhang, R. L., C. Zhang, et al. (2008). "Synergistic Effect of an Endothelin Type A Receptor Antagonist, S-0139, With rtPA on the Neuroprotection After Embolic Stroke." *Stroke*. Epub Ahead of Print. [Article Request Form](#)

From the Departments of Neurology and Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, Mich; Pharmaceutical Research Division, Shionogi & Co Ltd, Osaka, Japan; CNS Program & Clinical Development, Shionogi USA Inc, Florham Park, NJ; and the Department of Physics, Oakland University, Rochester, Mich.

**BACKGROUND AND PURPOSE:** Using a model of embolic stroke, the present study tested the hypothesis that blockage of endothelin-1 with S-0139, a specific endothelin type A receptor (ETA) antagonist, enhances the neuroprotective effect of recombinant tissue plasminogen activator (rtPA) by suppressing molecules that mediate thrombosis and blood brain barrier (BBB) disruption induced by ischemia and rtPA. **METHODS:** Rats (n=104) subjected to embolic middle cerebral artery (MCA) occlusion were randomly divided into 1 of 4 infusion groups with 26 rats per group: (1) the control group in which rats were administered saline, (2) the monotherapy rtPA group in which rtPA was intravenously administered at a dose of 10 mg/kg 4 hours after MCA occlusion, (3) the monotherapy S-0139 group in which S-0139 was intravenously given 2 hours after MCA occlusion, and (4) the combination of rtPA +S-0139 group in which S-0139 and rtPA were given 2 and 4 hours after MCA occlusion, respectively. Measurements of infarct volume and parenchymal hemorrhage, behavioral outcome, and immunostaining were performed on rats euthanized 1 and 7 days after stroke. **RESULTS:** The combination therapy of S-0139 and rtPA significantly ( $P<0.01$ ) reduced infarct volume (24.8+/-0.9% versus 33.8+/-1.5% in control) and hemorrhagic area (7.1+/-6.1 microm<sup>2</sup> versus 36.5+/-19.2 microm<sup>2</sup> in control) and improved functional recovery compared with control saline-treated animals. Immunostaining analysis revealed that the combination therapy had the synergistically suppressed ischemia- and rtPA-induced ICAM-1, protease-activated receptor 1 (PAR-1), as well as accumulation of platelets in cerebral microvessels. Furthermore, the combination treatment synergistically reduced loss of laminin, ZO1, and occludin in cerebral vessels. **CONCLUSIONS:** These data suggest that S-0139 provides the neuroprotection by suppressing ischemia- and rtPA-triggered molecules that evoke thrombosis and BBB disruption.

...

## Neurology

Zheng, X., F. Jiang, et al. (2008). "Sensitization of cerebral tissue in nude mice with photodynamic therapy induces ADAM17/TACE and promotes glioma cell invasion." *Cancer Lett* **265**(2): 177-87. [Article Request Form](#)

Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

In the present study, we tested the hypothesis that a mild cerebral tissue injury promotes subsequent glioma invasion via activation of the ADAM17-EGFR-PI3K-Akt pathway. Mild injury was induced by photodynamic therapy (PDT), which employs tissue-penetrating laser light exposure following systemic administration of a tumor-localizing photosensitizer. Athymic nude mice were treated with sublethal PDT (80 J/cm<sup>2</sup> with 2 mg/kg Photofrin). Hypoxic stress and ADAM17-EGFR-PI3K-Akt were measured using Western blot and immunostaining. Additional groups with/without pro-sublethal

PDT were subsequently implanted with U87 glioma tumor cell. Tumor invasion and ADAM17-EGFR-PI3K-Akt pathway in tumor area were measured. After a sublethal dose of PDT, HIF-1 $\alpha$  expression was increased by a factor of three in PDT-treated normal brain tissue compared to contralateral control brain tissue. PDT-treated brain tissue exhibited a significant increase in ADAM17, p-EGFR, p-Akt expression compared to non-treated tissue. ADAM17 positive area significantly increased from 1.78% to 10.89%. The percentage of p-EGFR and p-Akt positive cells significantly increased from 9.50% and 14.50% to 21.31% and 32.29%, respectively, PDT treatment significantly increased subsequent implanted U87 glioma cell invasion by 3.68-fold and increased ADAM17, EGFR, p-EGFR, Akt, p-Akt expression by 178%, 43.9%, 152.7%, 89.6%, and 164.2%, respectively, compared to control group. Our data showed that a sublethal sensitization of cerebral tissue with PDT significantly increased U87 cell invasion in nude mice, and that glioma cell invasion is highly correlated with activation of the ADAM17-EGFR-PI3K-Akt pathway ( $r=0.928, 0.775, 0.870, 0.872, \text{ and } 0.883$ , respectively), most likely via HIF-1 $\alpha$ .

...

## Neurosurgery

Xiong, Y., A. Mahmood, et al. (2008). "Histological and functional outcomes after traumatic brain injury in mice null for the erythropoietin receptor in the central nervous system." *Brain Res* **1230**: 247-57. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, 2799 W Grand Blvd., Detroit, MI 48202, USA.

Erythropoietin (EPO) and its receptor (EPOR), essential for erythropoiesis, are expressed in the nervous system. Recombinant human EPO treatment promotes functional outcome after traumatic brain injury (TBI) and stroke, suggesting that the endogenous EPO/EPOR system plays an important role in neuroprotection and neurorestoration. This study was designed to investigate effects of the EPOR on histological and functional outcomes after TBI. Experimental TBI was induced in adult EPOR-null and wild-type mice by controlled cortical impact. Neurological function was assessed using the modified Morris Water Maze and footfault tests. Animals were sacrificed 35 days after injury and brain sections stained for immunohistochemistry. As compared to the wild-type injured mice, EPOR-null mice did not exhibit higher susceptibility to TBI as exemplified by tissue loss in the cortex, cell loss in the dentate gyrus, impaired spatial learning, angiogenesis and cell proliferation. We observed that less cortical neurogenesis occurred and that sensorimotor function (i.e., footfault) was more impaired in the EPOR-null mice after TBI. Co-accumulation of amyloid precursor protein (axonal injury marker) and calcium was observed in the ipsilateral thalamus in both EPOR-null and wild-type mice after TBI with more calcium deposits present in the wild-type mice. This study demonstrates for the first time that EPOR null in the nervous system aggravates sensorimotor deficits, impairs cortical neurogenesis and reduces thalamic calcium precipitation after TBI.

...

## Neurosurgery

Yunker, C. K., W. Golembieski, et al. (2008). "SPARC-induced increase in glioma matrix and decrease in vascularity are associated with reduced VEGF expression and secretion." *Int J Cancer* **122**(12): 2735-43. [PDF Full-Text](#)

Barbara Jane Levy Laboratory of Molecular Neuro-Oncology, Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA.

Glioblastomas are heterogeneous tumors displaying regions of necrosis, proliferation, angiogenesis, apoptosis and invasion. SPARC, a matricellular protein that negatively regulates angiogenesis and cell proliferation, but enhances cell deadhesion from matrix, is upregulated in gliomas (Grades II-IV). We previously demonstrated that SPARC promotes invasion while concomitantly decreasing tumor growth, in part by decreasing proliferation of the tumor cells. In other cancer types, SPARC has been shown to influence tumor growth by altering matrix production, and by decreasing angiogenesis via interfering with the VEGF-VEGFR1 signaling pathway. We therefore examined whether the SPARC-induced decrease in glioma tumor growth was also, in part, due to alterations in matrix and/or decreased vascularity, and assessed SPARC-VEGF interactions. The data demonstrate that SPARC upregulates glioma matrix, collagen I is a constituent of the matrix and SPARC promotes collagen fibrillogenesis. Furthermore, SPARC suppressed glioma vascularity, and this was accompanied by decreased VEGF expression and secretion, which was, in part, due to reduced VEGF165 transcript abundance. These data indicate that SPARC modulates glioma growth by altering the tumor microenvironment and by suppressing tumor vascularity through suppression of VEGF expression and secretion. These experiments implicate a novel mechanism, whereby SPARC regulates VEGF function by limiting the available growth factor. Because SPARC is considered to be a therapeutic target for gliomas,

a further understanding of its complex signaling mechanisms is important, as targeting SPARC to decrease invasion could undesirably lead to the growth of more vascular and proliferative tumors.

...

## Pathology

Raab, S. S., B. A. Jones, et al. (2008). "The effect of continuous monitoring of cytologic-histologic correlation data on cervical cancer screening performance." *Arch Pathol Lab Med* **132**(1): 16-22. [PDF Full-Text](#)

University of Pittsburgh School of Medicine, UPMC Shadyside Hospital, Department of Pathology, 5150 Centre Ave, Pittsburgh, PA 15232, USA. [raabss@upmc.edu](mailto:raabss@upmc.edu)

CONTEXT: The use of Papanicolaou (Pap) test cytologic-histologic correlation in quality improvement activities is not well studied. OBJECTIVE: To determine if continuous monitoring of correlation data improves performance. DESIGN: Participants in the College of American Pathologists Q-Tracks program (213 laboratories) self-reported the number of Pap test-histologic biopsy correlation discrepancies every quarter for up to 8 years. A mixed linear model determined if the length of participation in the Q-Tracks program was associated with improved performance. Main outcome measures were predictive value of a positive Pap test, Pap test sensitivity, sampling sensitivity, and proportion of positive histologic diagnoses following a Pap test diagnosis of atypical squamous cells or atypical glandular cells. RESULTS: Institutions evaluated 287,570 paired Pap test-histologic correlation specimens and found 98,424 (34.2%) true-positive Pap test correlations, 19,006 (6.6%) false-positive Pap test correlations, and 6575 (2.3%) false-negative Pap test correlations. The mean predictive value of a positive Pap test, sensitivity, screening and interpretive sensitivity, sampling sensitivity, and proportion of positive histologic diagnoses following a Pap test diagnosis of atypical squamous or glandular cells were 83.6%, 93.7%, 99.2%, 94.2%, 60.3%, and 38.8%, respectively. Longer participation was significantly associated with a higher predictive value of a positive Pap test ( $P = .01$ ), higher Pap test sensitivity ( $P = .002$ ), higher Pap test sampling sensitivity ( $P = .03$ ), and higher proportion of positive histologic diagnoses for a Pap test diagnosis of atypical squamous cells ( $P < .001$ ). CONCLUSIONS: Long-term monitoring of cytologic-histologic correlation is associated with improvement in cytologic-histologic correlation performance.

...

## Pathology

Tworek, J. A., B. A. Jones, et al. (2007). "The value of monitoring human papillomavirus DNA results for Papanicolaou tests diagnosed as atypical squamous cells of undetermined significance: a College of American Pathologists Q-Probes study of 68 institutions." *Arch Pathol Lab Med* **131**(10): 1525-31. [PDF Full-Text](#)

Department of Pathology, St Joseph Mercy Hospital, 5301 E Huron River Dr, PO Box 995, Ann Arbor, MI 48106-0995, USA. [joetworek@yahoo.com](mailto:joetworek@yahoo.com)

CONTEXT: Papanicolaou (Pap) tests are often diagnosed as atypical squamous cells of undetermined significance (ASC-US). Human papillomavirus (HPV) DNA testing has been proposed as a quality metric for this diagnosis. OBJECTIVE: To measure the frequency of HPV positivity in Pap tests diagnosed as ASC-US and to examine laboratory variables that are associated with institutional deviation from the mean percent of HPV positivity. DESIGN: As part of a College of American Pathologist Q-Probes program, 68 participating laboratories retrospectively identified approximately 50 consecutive ASC-US Pap tests that had HPV testing results. RESULTS: The mean percentage of HPV positivity for ASC-US was 43.74% among institutions surveyed, but it had a broad distribution, with an SD of 17.77%. Associations were found for lower difference of the institutional mean from the surveyed interinstitutional mean percentage of positive HPV with (1) higher numbers of Pap tests in the past year that had HPV testing, (2) in-house HPV testing, and (3) teaching hospitals. All 3 factors correlated with a larger volume of Pap tests per institution. An association was found between patient age and the probability of a positive HPV result, indicating a dependence upon prevalence of HPV. CONCLUSIONS: Larger volumes of Pap tests may offer an opportunity to gain greater comfort in interpreting Pap tests. While there is significant variability in interinstitutional HPV-positive rates in ASC-US Pap tests, monitoring the HPV-positive rate in ASC-US Pap tests is a valuable broad measure of quality. Performance beyond 2 SDs of the mean should prompt reassessment of diagnostic criteria used in the evaluation of Pap tests and/or investigation of the prevalence of HPV positivity in the population from which the Pap tests are obtained.

...

## Pulmonary and Critical Care Medicine

Burke, R. R., C. H. Stone, et al. (2008). "Racial Differences in Sarcoidosis Granuloma Density." *Lung*. EPub Ahead of Print. [PDF Full-Text](#)

Division of Pulmonary, Critical Care and Sleep Medicine, Henry Ford Hospital, Detroit, MI, 48202, USA, [RBURKE1@hfhs.org](mailto:RBURKE1@hfhs.org).

**Study Objectives** While sarcoidosis generally inflicts a greater morbidity on African-American compared with Caucasian patients, no studies have examined whether racial differences exist in the intensity of the histologic hallmark of sarcoidosis, noncaseating granulomas. **Design and Setting** The study was conducted as a retrospective case series in a tertiary referral center. **Patients** The study included 187 patients with histopathologic confirmation of sarcoidosis by trans- and/or endobronchial biopsy between July 1991 and December 2001. **Measurements and Results** Granuloma density was the average number of granulomas per biopsy piece on the slide with the most intense granulomatous inflammation at fourfold magnification. Overall, African-American patients had a twofold greater median granuloma density than Caucasians ( $p = 0.005$ ). In a negative binomial multivariate model, radiographic pattern had the strongest association with granuloma density, with Scadding stage II and III patients having adjusted granuloma densities of 60% ( $p = 0.005$ ) and 105% ( $p = 0.0001$ ) higher than stage I patients. In the specific-tissue types, radiographic stage-adjusted granuloma densities in African-American patients were 49% greater in bronchial tissue ( $p = 0.03$ ), but only a 27% greater in alveolar tissue ( $p = 0.51$ ). **Conclusions** A greater granuloma density in bronchiolar lung tissue of African-American sarcoidosis patients may explain racial differences in diagnostic yield by lung biopsy and disease severity at diagnosis. This association persists even after controlling for Scadding radiographic stage, a measure of disease severity strongly associated with granuloma density.

...

## Radiation Oncology

Barton, K. N., H. Stricker, et al. (2008). "Phase I Study of Noninvasive Imaging of Adenovirus-mediated Gene Expression in the Human Prostate." *Mol Ther*. EPub Ahead of Print. [Article Request Form](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan, USA.

To monitor noninvasively potentially therapeutic adenoviruses for cancer, we have developed a methodology based on the sodium iodide symporter (NIS). Men with clinically localized prostate cancer were administered an intraprostatic injection of a replication-competent adenovirus, Ad5-yCD/utTK(SR39)rep-hNIS, armed with two suicide genes and the NIS gene. NIS gene expression (GE) was imaged noninvasively by uptake of  $Na(99m)TcO(4)$  in infected cells using single photon emission-computed tomography (SPECT). The investigational therapy was safe with 98% of the adverse events being grade 1 or 2. GE was detected in the prostate in seven of nine (78%) patients at  $1 \times 10^{12}$  virus particles (vp) but not at  $1 \times 10^{11}$  vp. Volume and total amount of GE was quantified by SPECT. Following injection of  $1 \times 10^{12}$  vp in  $1 \text{ cm}^3$ , GE volume (GEV) increased to a mean of  $6.6 \text{ cm}^3$ , representing, on average, 18% of the total prostate volume. GEV and intensity peaked 1-2 days after the adenovirus injection and was detectable in the prostate up to 7 days. Whole-body imaging demonstrated intraprostatic gene expression, and there was no evidence of extraprostatic dissemination of the adenovirus by SPECT imaging. The results demonstrate that noninvasive imaging of adenovirus-mediated gene therapy in humans is feasible and safe. *Molecular Therapy* (2008); doi:10.1038/mt.2008.172.

...

## Radiation Oncology

Jin, J. Y., M. Ajlouni, et al. (2008). "Utilize target motion to cover clinical target volume (ctv) - a novel and practical treatment planning approach to manage respiratory motion." *Radiother Oncol*. EPub Ahead of Print. [Article Request Form](#)

Department of Radiation Oncology, Henry Ford Hospital, USA.

**PURPOSE:** To use probability density function (PDF) to model motion effects and incorporate this information into treatment planning for lung cancers. **MATERIAL AND METHODS:** PDFs were calculated from the respiratory motion traces of 10 patients. Motion effects were evaluated by convolving static dose distributions with various PDFs. Based on a differential

dose prescription with relatively lower dose to the clinical target volume (CTV) than to the gross tumor volume (GTV), two approaches were proposed to incorporate PDFs into treatment planning. The first approach uses the GTV-based internal target volume (ITV) as the planning target volume (PTV) to ensure full dose to the GTV, and utilizes the motion-induced dose gradient to cover the CTV. The second approach employs an inhomogeneous static dose distribution within a minimized PTV to best match the prescription dose gradient. RESULTS: Motion effects on dose distributions were minimal in the anterior-posterior (AP) and lateral directions: a 10-mm motion only induced about 3% of dose reduction in the peripheral target region. The motion effect was remarkable in the cranial-caudal direction. It varied with the motion amplitude, but tended to be similar for various respiratory patterns. For the first approach, a 10-15mm motion would adequately cover the CTV (presumed to be 60-70% of the GTV dose) without employing the CTV in planning. For motions <10-mm, an additional PTV with a margin inversely related to the motion was needed to cover the CTV. The second approach was used for motions >15-mm. An example of inhomogeneous static dose distribution in a reduced PTV was given, and it showed significant dose reduction in the normal tissue without compromising target coverage. CONCLUSIONS: Respiratory motion-induced dose gradient can be utilized to cover the CTV and minimize the lung dose without the need for more sophisticated technologies.

...

## Radiation Oncology

Kim, J. H., S. L. Brown, et al. (2008). "Mechanisms of radiation-induced brain toxicity and implications for future clinical trials." *J Neurooncol* **87**(3): 279-86. [PDF Full-Text](#)

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

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.

...

## Sleep Medicine

Roehrs, T. and T. Roth (2008). "Caffeine: sleep and daytime sleepiness." *Sleep Med Rev* **12**(2): 153-62. [PDF Full-Text](#)

Sleep Disorders and Research Center, Henry Ford Hospital, 2799 W Grand Blvd, CFP-3, Detroit, MI 48202, USA. [taroehrs@aol.com](mailto:taroehrs@aol.com)

Caffeine is one of the most widely consumed psychoactive substances and it has profound effects on sleep and wake function. Laboratory studies have documented its sleep-disruptive effects. It clearly enhances alertness and performance in studies with explicit sleep deprivation, restriction, or circadian sleep schedule reversals. But, under conditions of habitual sleep the evidence indicates that caffeine, rather than enhancing performance, is merely restoring performance degraded by sleepiness. The sleepiness and degraded function may be due to basal sleep insufficiency, circadian sleep schedule reversals, rebound sleepiness, and/or a withdrawal syndrome after the acute, over-night, caffeine discontinuation typical of most studies. Studies have shown that caffeine dependence develops at relatively low daily doses and after short periods of regular daily use. Large sample and population-based studies indicate that regular daily dietary caffeine intake is associated with disturbed sleep and associated daytime sleepiness. Further, children and adolescents, while reporting lower daily, weight-corrected caffeine intake, similarly experience sleep disturbance and daytime sleepiness associated with

their caffeine use. The risks to sleep and alertness of regular caffeine use are greatly underestimated by both the general population and physicians.

...

### **Sleep Medicine**

Roth, T. (2008). "Hypnotic use for insomnia management in chronic obstructive pulmonary disease." *Sleep Med.* EPub Ahead of Print. [PDF Full-Text](#)

Sleep Disorders and Research Center, Henry Ford Hospital, 2799 West Grand Boulevard, CFP-3 Detroit, MI 48202, USA.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. Because of the chronic nature of the disease, optimal care for patients includes successful treatment of comorbidities that accompany COPD, including insomnia. Insomnia symptoms and associated disruption of sleep are prevalent in COPD patients but treatment with traditional benzodiazepines may compromise respiratory function. This review summarizes the efficacy and safety consideration of current drugs available for the treatment of insomnia in COPD patients including benzodiazepines, non-benzodiazepine receptor agonists such as eszopiclone, zolpidem, and zaleplon, sedating antidepressants such as trazodone, and the melatonin receptor agonist ramelteon.

...

### **Surgery**

Kharbutli, B. and V. Velanovich (2008). "Management of Preoperatively Suspected Choledocholithiasis: A Decision Analysis." *J Gastrointest Surg.* EPub Ahead of Print. [PDF Full-Text](#)

Division of General Surgery, K-8, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI, 48202, USA.

**BACKGROUND:** The management of symptomatic or incidentally discovered common bile duct (CBD) stones is still controversial. Of patients undergoing elective cholecystectomy for symptomatic cholelithiasis, 5-15% will also harbor CBD stones, and those with symptoms suggestive of choledocholithiasis will have an even higher incidence. Options for treatment include preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (ERCP/ES) followed by laparoscopic cholecystectomy, laparoscopic cholecystectomy with intraoperative cholangiogram (LC/IOC), followed by either laparoscopic common bile duct exploration (LCBDE) or placement of a common bile duct double-lumen catheter with postoperative management. The purpose of this analysis was to determine the optimal management of such patients. **METHODS:** A decision analysis was performed to analyze the management of patients with suspected common bile duct stones. The basic choice was between preoperative ERCP/ES followed by LC, LC/IOC followed by LCBDE, or common duct double-lumen catheter (Fitzgibbons tube) placement with either expectant management or postoperative ERCP/ES. Data on morbidity and mortality was obtained from the literature. Sensitivity analysis was done varying the incidence of positive CBD stones on IOC with associated morbidity and mortality. **RESULTS:** One-stage management of symptomatic CBD stones with LC/LCBDE is associated with less morbidity and mortality (7% and 0.19%) than two-stage management utilizing preoperative ERCP/ES (13.5% and 0.5%). Sensitivity analysis shows that there is an increase in morbidity and mortality for LC/LCBDE as the incidence of positive IOC increases but are still less than two-stage management even with a 100% positive IOC (9.4%, 0.5%). If a double-lumen catheter is to be used for positive IOC, the morbidity would be higher than two-stage management only if the positive IOC incidence is more than 65% but still with no mortality. **CONCLUSION:** LCBDE has lower morbidity and mortality rates compared to preoperative ERCP/ES in the management of patients with suspected CBD stones even if the chance of CBD stones reaches 100%. Using a common duct double-lumen catheter may be considered if LCBDE is not feasible and the chance of CBD stone is less than 65%.

...

### **Surgery**

Vanderlan, W. B., M. S. Abouljoud, et al. (2008). "Experience with recipient splenic artery inflow in adult liver transplantation: a case series." *Cases J* 1(1): 82. [PDF Full-Text](#)

Department of Surgery, Division of Transplant Surgery and Hepatobiliary Surgery, Henry Ford Hospital, 2799 West Grand Boulevard (CFP-2), Detroit, MI, 48202, USA. [blakevanderlan@yahoo.com](mailto:blakevanderlan@yahoo.com).

ABSTRACT: INTRODUCTION: Hepatic artery thrombosis following orthotopic liver transplant is one of the most common reasons for early graft failure. Meticulous reconstitution of hepatic artery flow remains essential for good outcomes. Prior surgery, body habitus, hepatic artery inadequacy and anatomic differences can complicate hepatic artery revascularization. CASE PRESENTATION: We report a single institution's experience, from January 1996 to January 2007, using splenic artery inflow in seven patients with inadequate native hepatic arteries. CONCLUSION: End-to-side anastomosis was associated with postanastomotic intimal hyperplasia. End-to-end anastomosis provided effective hepatic inflow, demonstrated splenic and pancreatic safety, and was not associated with the intimal hyperplasia experienced with end-to-side anastomosis.

...

## Surgery

Velanovich, V. (2008). "Quality of Life and Symptomatic Response to Gastric Neurostimulation for Gastroparesis." *J Gastrointest Surg*. Epub Ahead of Print. [PDF Full-Text](#)

Division of General Surgery, K&H; Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI, 48202, USA, [vvelano1@hfhs.org](mailto:vvelano1@hfhs.org).

BACKGROUND: Gastroparesis can be a difficult problem with patients suffering from nausea, vomiting, bloating, and pain intractable to medical management. Gastric neurostimulation has been developed as an adjunctive treatment for patients with diabetic and idiopathic gastroparesis unresponsive to pharmacologic and dietary treatment. The purpose of this study is to report symptomatic and quality-of-life response to gastric neurostimulation. METHODS: This study was approved by the institutional review board, and patients had informed consent. The gastric neurostimulation device (Enterra therapy, Medtronic, Inc., Minneapolis, MN, USA) is approved by the Food and Drug Administration under the Humanitarian Device Exemption. Candidates for placement were patients with either idiopathic or diabetic gastroparesis who had symptomatic failure to dietary changes and to prokinetic and antiemetic drugs. Before placement, the patients' symptoms were recorded, and patients completed the Gastrointestinal Symptom Rating Scale (GSRS, three domains: dyspeptic syndrome, indigestion syndrome, and bowel dysfunction syndrome) and the Short Form-36 (SF-36, eight domains: physical functioning, role-physical, role-emotional, bodily pain, vitality, mental health, social functioning, general health, plus a health transition item). The device was surgically placed using a hybrid laparoscopic/open technique. Patients were followed and adjustments made on the device until satisfactory symptom control was achieved. At that time, patients completed both the GSRS and SF-36, and comparisons were made to preoperative values. RESULTS: Forty-two patients had the device placed, 29 women, aged 41 (SD +14) years, 24 diabetic patients, 17 idiopathic patients, one postgastrectomy patient. Median follow-up was 12 months (range 1-42 months). There was a 2% immediate postoperative morbidity rate and 7% long-term morbidity rate (device extrusion). Thirty-one patients (74%) responded to gastric neurostimulation of variable degrees. Eleven patients had no response or had worsening symptoms. Of the patients who responded, there were statistically significant improvements in all three domains of the GSRS. Median scores (with interquartile ranges): dyspeptic syndrome, 9 (7-11.5) to 4 (2.5-6),  $p = 0.02$ ; indigestion syndrome, 5 (2-7) to 4 (0-5),  $p = 0.05$ ; bowel dysfunction syndrome, 3 (2-3) to 1 (0-1),  $p = 0.01$ . In the SF-36, there were statistically significant improvement in the health transition item, 4 (4-5) to 1.5 (1-3),  $p = 0.01$ ; and social functioning domain, 25 (12.5-62.5) to 75 (50-87.5),  $p = 0.03$ . CONCLUSIONS: Three quarters of gastroparesis patients responded to gastric neurostimulation to variable degrees. Gastrointestinal-specific symptoms are improved in responders. Patients felt that their health and social functioning (SF) improved, although there was no significant difference in the other domains. These results are encouraging considering that these patients had intractable symptoms with no other effective treatments available.

...

## Urology

Bhandari, M. and S. Siva (2008). "Re: Radical Nephrectomy for pT1a Renal Masses May be Associated With Decreased Overall Survival Compared With Partial Nephrectomy R. H. Thompson, S. A. Boorjian, C. M. Lohse, B. C. Leibovich, E. D. Kwon, J. C. Cheville and M. L. Blute *J Urol* 2008; 179: 468-473." *J Urol*. Epub Ahead of Print. [PDF Full Text](#)

Vattikuti Urology Institute, Henry Ford Hospital System, Detroit, Michigan.

...

## Urology

Eun, D., A. Bhandari, et al. (2008). "A Novel Technique for Creating Solid Renal Pseudotumors and Renal Vein-Inferior Vena Caval Pseudothrombus in a Porcine and Cadaveric Model." *J Urol*. EPub Ahead of Print. [PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan.

**PURPOSE:** We developed a simple means to replicate kidney tumors in an animal and cadaver model that could be used to create pseudotumors of different sizes and locations for use in surgical training. **MATERIALS AND METHODS:** Various substances were injected ex vivo into the parenchyma of porcine kidneys to identify an optimal pseudotumor model. Renal pseudotumors were created percutaneously and endoscopically using 8 live pigs and a human cadaver model. A renal vein pseudothrombus porcine model was also created by injecting pseudothrombus material into the renal vein after renal hilar clamping. Procedures performed on pseudotumors included robotic partial nephrectomy, percutaneous biopsy and robotic nephrectomy with renal vein thrombectomy. All specimens were analyzed after resection. **RESULTS:** The most ideal pseudotumor models were created from a mixture of gelatin, Metamucil(R) and methylene blue (metagel) or from Kromopan(R) hydrocolloid. We created 33 tumors 0.5 to 3.5 cm in size (mean 2.8). All tumors were a solid palpable mass on gross examination and ultrasonography revealed clearly visible hyperechoic lesions in 30 of 33. A renal vein tumor pseudothrombus model was successfully created in 3 pigs. We successfully performed robotic excision of pseudotumors, including partial nephrectomy for 16 and radical nephrectomy with renal vein thrombectomy for 3. Percutaneous needle core biopsy under ultrasound guidance was also successfully performed. **CONCLUSIONS:** We describe what is to our knowledge a novel technique of creating solid renal tumors and tumor thrombi that can be used for training in minimally invasive kidney surgery.

...

## Urology

Laungani, R., N. Patil, et al. (2008). "Robotic-Assisted Ureterovaginal Fistula Repair: Report of Efficacy and Feasibility." *J Laparoendosc Adv Surg Tech A*. EPub Ahead of Print. [Article Request Form](#)

Department of Urology, Vattikutti Urology Institute, Henry Ford Hospital, Detroit, Michigan.

**Abstract Introduction and Objective:** Iatrogenic ureteral injuries are most commonly seen following pelvic and gynecologic surgery. If early conservative endoscopic management fails, surgical correction may be necessary. In this paper, we report 3 cases of the development of ureterovaginal fistula (UVF) after a total abdominal hysterectomy. All 3 cases underwent a robotic-assisted surgical correction. **Materials and Methods:** Three female patients (37, 50, and 66 years) were diagnosed with a left-sided ureterovaginal fistula following an abdominal hysterectomy. All patients reported urinary leakage per vagina and were diagnosed on excretory urography. All patients underwent robotic repair of ureterovaginal fistula along with ureteral reimplantation. **Results:** In all patients, a standard six-port approach was used. Robotic endowrist movement and three-dimensional views aided significantly in the dissection of the viable ureter from periureteral fibrosis and scar. Prior to ureterovesical anastomosis, a double J pigtail stent was inserted intracorporeally through the left 5-mm assistant port. In all cases, the robotic ureteroneocystostomy was completed without complication. Total console surgical time ranged from 62 to 118 minutes. The Foley catheter was removed 24-48 hours after surgery. All patients were discharged completely dry with an indwelling stent in situ. **Conclusions:** We report a case series of pure robotic ureteroneocystostomy for repair of complex UVF. The da Vinci((R)) robotic surgical system provides a tremendous advantage for the gross identification of viable structures within dense scar tissue as well as the identification of healthy ureter for reimplantation. We strongly recommend an early repair of these fistulae with robotic assistance to reduce the period of morbidity.

...

## Urology

Menon, M. and M. Bhandari (2008). "Unhappy patients: musings of two surgical nihilists." *Eur Urol* **54**(4): 723-5. [PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Departments of Urology, Case Western University School of Medicine, New York University School of Medicine and University of Toledo School of Medicine, United States.

...

## Urology

Rogers, C., R. Laungani, et al. (2008). "*Robotic nephrectomy for the treatment of benign and malignant disease.*" *BJU Int.* EPub Ahead of Print. [PDF Full-Text](#)

Henry Ford Hospital, Vattikuti Urology Institute, Detroit, MI, USA.

**OBJECTIVES** To report our experience and describe our technique of robotic nephrectomy. **PATIENTS AND METHODS** We retrospectively evaluated 42 patients who underwent robotic nephrectomy at our institution from January 2004 to March 2008. Variables assessed included patient age, body mass index, operative duration, estimated blood loss (EBL), complications, hospital stay, analgesia requirements and specimen pathology. Radical nephrectomy (RN) was performed for suspected malignant disease and simple nephrectomy (SN) was performed for benign disease. **RESULTS** In all, 42 patients with a mean (range) age of 59.4 (17-38) years, underwent robotic nephrectomy (RN 35, SN seven) using a transperitoneal (39) or retroperitoneal (three) approach. The mean operative console time was 158 min, mean EBL was 223 mL, mean tumour size was 5.1 cm, and the mean hospital stay was 2.4 days. Renal hilar vessels were controlled using robotic suture ligation (25), robotic haemolock clips (12), or laparoscopic staplers (five). No patients required open conversion. One morbidly obese patient developed a wound dehiscence (complication rate 2.6%). On final tumour pathology, the RN specimens included 34 renal cell carcinomas (clear cell 23, papillary nine, chromophobe two) and an oncocytoma. The SN specimens showed chronic xanthogranulomatous pyelonephritis (four) and atrophic kidneys (three). All surgical margins were negative for malignancy with no evidence of tumour recurrence at a mean (range) follow-up of 15.7 (1-51) months. **CONCLUSIONS** Robotic nephrectomy is a safe and feasible option for minimally invasive surgical removal of the kidney for benign and malignant conditions and can be performed through a transperitoneal or retroperitoneal approach.

...

## Urology

Sivanandam, A., S. Siva, et al. (2008). "*Variance inflation in sequential calculations of body surface area, plasma volume, and prostate-specific antigen mass.*" *BJU Int.* EPub Ahead of Print. [PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

**OBJECTIVE** To assess the magnitude of variability among 11 formulae for human body surface area (BSA) and then among eight for plasma volume (PV), as used to represent physiological indices for body metabolism, drug dosages and body fluid management, and to evaluate the potential cumulative effect of variance inflation with prostate-specific antigen (PSA) mass as an endpoint. **PATIENTS AND METHODS** In 3020 men undergoing robotic radical prostatectomy (RRP) at the Vattikuti Urology Institute between 2001 and 2008, the variation in BSA and PV formulae was calculated, as well as PSA mass, using analysis of variance (anova), Bland-Altman plots, linear regression, and correlation analyses. **RESULTS** For estimating BSA, anova indicated significant variance among the 11 formulae used ( $P < 0.001$ ) with a between-groups variance of 5.45. Bland-Altman plots reported bias when the Dubois formula was compared to other BSA formulae. Furthermore the anova for PV, with BSA as a predictor, indicated significant variance among the eight formulae used ( $P < 0.001$ ), with a mean between-group variance of 444.4 and a mean inflation factor of 81.5. Scatter plots between one PV formula (Boer) and others had a good linear fit. For PSA mass, anova indicated significant variance ( $P < 0.001$ ) using PV as a predictor, with a mean between-group variance of 16 799.6 and a mean variance inflation factor of 37.8. **CONCLUSIONS** There is significant variation in the BSA calculated by commonly used formulae. This variation is carried over and further magnified in the sequential calculation of PV and PSA mass. Hence arbitrary selection of BSA and PV formulae is likely to affect inferences.

...

# HFHS Publication List Sladen Library

<http://www.henryfordconnect.com/sliden.cfm?id=436>

If you are interested in receiving this list of HFHS Publications on a monthly basis, please fill out the following information:

Name \_\_\_\_\_

Department \_\_\_\_\_

Phone Number \_\_\_\_\_

Email \_\_\_\_\_

Do you want to receive it:

\_\_\_\_\_ Via email (Recommended format – includes links to full-text if available)

\_\_\_\_\_ Via interdepartmental mail

Please return to:

Valerie Reid  
HFH Sladen Library, K-17  
(313) 916-2550  
(313) 874-4730 Fax  
[vreid1@sladen.hfhs.org](mailto:vreid1@sladen.hfhs.org)