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

Behavioral Services

Lajiness-O'Neill, R. (2009). "Introduction to neuropsychology, 2nd edition." Journal of Clinical and Experimental Neuropsychology **31**(8): 1012-1014.

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[Lajiness-O'Neill, Rene] Eastern Michigan Univ, Dept Psychol, Ypsilanti, MI 48197 USA.
[Lajiness-O'Neill, Rene] Henry Ford Hlth Sci, Div Neuropsychol, Dept Behav Hlth, Detroit, MI USA.

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Biostatistics & Research Epidemiology

Bock, C. H., A. G. Schwartz, J. J. Ruterbusch, A. M. Levin, C. Neslund-Dudas, S. J. Land, A. S. Wenzlaff, D. Reich, P. McKeigue, W. Chen, E. I. Heath, I. J. Powell, R. A. Kittles and B. A. Rybicki (2009). "Results from a prostate cancer admixture mapping study in African-American men." Human Genetics **126**(5): 637-642. [PDF Full-Text](#)

[Bock, Cathryn Hufford; Schwartz, Ann G.; Land, Susan J.; Chen, Wei; Heath, Elisabeth I.; Powell, Isaac J.] Wayne State Univ, Sch Med, Detroit, MI 48201 USA. [Bock, Cathryn Hufford; Schwartz, Ann G.; Ruterbusch, Julie J.; Wenzlaff, Angela S.; Chen, Wei; Heath, Elisabeth I.; Powell, Isaac J.; Rybicki, Benjamin A.] Karmanos Canc Inst, Detroit, MI 48201 USA. [Levin, Albert M.; Neslund-Dudas, Christine; Rybicki, Benjamin A.] Henry Ford Hlth Syst, Detroit, MI 48202 USA. [Reich, David] Harvard Univ, Sch Med, Boston, MA 02115 USA. [Reich, David] Broad Inst Harvard & MIT, Cambridge, MA 02142 USA. [McKeigue, Paul] Univ Edinburgh, Western Gen Hosp, Edinburgh EH4 2XU, Midlothian, Scotland. [Kittles, Rick A.] Univ Chicago, Chicago, IL 60637 USA.

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There are considerable racial disparities in prostate cancer risk, with a 60% higher incidence rate among African-American (AA) men compared with European-American (EA) men, and a 2.4-fold higher mortality rate in AA men than in EA men. Recently, studies have implicated several African-ancestry associated prostate cancer susceptibility loci on chromosome 8q24. In the current study, we performed admixture mapping in AA men from two independent case-control studies of prostate cancer to confirm the 8q24 ancestry association and also identify other genomic regions that may harbor prostate cancer susceptibility genes. A total of 482 cases and 261 controls were genotyped for 1,509 ancestry informative markers across the genome. The mean estimated individual admixture proportions were 20% European and 80% African. The most significant

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observed increase in European ancestry occurred at rs2141360 on chromosome 7q31 in both the case-only ($P = 0.000035$) and case-control analyses. The most significant observed increase in African ancestry across the genome occurred at a locus on chromosome 5q35 identified by SNPs rs7729084 (case-only analysis $P = 0.002$), and rs12474977 (case-control analysis $P = 0.004$), which are separated by 646 kb and were adjacent to one another on the panel. On chromosome 8, rs4367565 was associated with the greatest excess African ancestry in both the case-only and case-control analyses (case-only and case-control $P = 0.02$), confirming previously reported African-ancestry associations with chromosome 8q24. In conclusion, we confirmed ancestry associations on 8q24, and identified additional ancestry-associated regions potentially harboring prostate cancer susceptibility loci.

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Biostatistics & Research Epidemiology

Bowles, E. J. A., L. Tuzzio, D. P. Ritzwoller, A. E. Williams, T. Ross, E. H. Wagner, C. Neslund-Dudas, A. Altschuler, V. Quinn, M. Hornbrook and L. Nekhlyudov (2009).

"Accuracy and Complexities of Using Automated Clinical Data for Capturing Chemotherapy Administrations Implications for Future Research." *Medical Care* **47**(10): 1091-1097. [PDF Full-Text](#)

[Bowles, Erin J. Aiello; Tuzzio, Leah; Ross, Tyler; Wagner, Edward H.] Grp Hlth Cooperat Puget Sound, Grp Hlth Ctr Hlth Studies, Seattle, WA 98101 USA. [Ritzwoller, Debra P.] Kaiser Permanente Colorado, Inst Hlth Res, Denver, CO USA. [Williams, Andrew E.] Kaiser Permanente Hawaii, Ctr Hlth Res, Honolulu, HI USA. [Neslund-Dudas, Christine] Henry Ford Hlth Syst, Dept Biostat & Res Epidemiol, Detroit, MI USA. [Altschuler, Andrea] Kaiser Permanente No Calif, Div Res, Oakland, CA USA. [Quinn, Virginia] Kaiser Permanente So Calif, Dept Res & Evaluat, Pasadena, CA USA. [Hornbrook, Mark] Kaiser Permanente NW, Ctr Hlth Res, Portland, OR USA. [Nekhlyudov, Larissa] Harvard Univ, Sch Med, Harvard Pilgrim Hlth Care, Dept Ambulatory Care & Prevent, Boston, MA USA.

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Background: Chemotherapy data are important to almost any study on cancer prognosis and outcomes. However, chemotherapy data obtained from tumor registries may be incomplete, and abstracting chemotherapy directly from medical records can be expensive and time consuming. Methods: We evaluated the accuracy of using automated clinical data to capture chemotherapy administrations in a cohort of 757 ovarian cancer patients enrolled in 7 health plans in the HMO Cancer Research Network. We calculated sensitivity and specificity with 95% confidence intervals of chemotherapy administrations extracted from 3 automated clinical data sources (Health Care Procedure Coding System, National Drug Codes, and International Classification of Diseases) compared with tumor registry data and medical chart data. Results: Sensitivity of all 3 data sources varied across health plans from 79.4% to 95.2% when compared with tumor registries, and 75.0% to 100.0% when compared with medical charts. The sensitivities using a combination of 3 data sources were 88.6% (95% confidence intervals: 85.7-91.1) compared with tumor registries and 89.5% (78.5-96.0) compared with medical records; specificities were 91.5% (86.4-95.2) and 90.0% (55.5-99.7), respectively. There was no difference in accuracy between women aged <65 and ≥ 65 years. Using one set of codes alone (eg, Health Care Procedure Coding System alone) was insufficient for capturing chemotherapy data at most health plans. Conclusions: While automated data systems are not without limitations, clinical codes used in combination are useful in capturing chemotherapy more comprehensively than tumor registry and without the need for costly medical record abstraction.

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Biostatistics & Research Epidemiology

Cassidy-Bushrow, A. E., L. F. Bielak, A. D. Rule, P. F. Sheedy, S. T. Turner, V. D. Garovic and P. A. Peyser (2009). "Hypertension during Pregnancy is Associated with Coronary Artery Calcium Independent of Renal Function." *Journal of Womens Health* **18**(10): 1709-1716. [Article Request Form](#)

[Bielak, Lawrence F.; Peyser, Patricia A.] Univ Michigan, Dept Epidemiol, Ann Arbor, MI 48109 USA. [Cassidy-Bushrow, Andrea E.] Henry Ford Hosp, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA. [Rule, Andrew D.; Turner, Stephen T.; Garovic, Vesna D.] Mayo Clin & Mayo Fdn, Dept Internal Med, Div Nephrol & Hypertens, Rochester, MN 55905 USA. [Sheedy, Patrick F., II] Mayo Clin & Mayo Fdn, Dept Diagnost Radiol, Rochester, MN 55905 USA.

Background: Hypertension during pregnancy (HDP) increases the risk of future coronary heart disease (CHD), but it is unknown whether this association is mediated by renal injury. Reduced renal function is both a complication of HDP and a risk factor for CHD. Methods: Logistic regression models were fit to examine the association between a history of HDP and the presence and extent of coronary artery calcification (CAC), a measure of subclinical coronary artery atherosclerosis, in 498 women from the Epidemiology of Coronary Artery Calcification Study (mean age 63.3+/-9.3 years). Results: Fifty-two (10.4%) women reported a history of HDP. After adjusting for age at time of study participation, HDP was associated with increased serum creatinine later in life ($p=0.014$). HDP was positively associated with the presence of CAC after adjusting for age at time of study participation ($OR=2.7$, 95% CI 1.4-5.4). This association was slightly attenuated with adjustment for body size and blood pressure ($OR=2.4$, 95% CI 1.2-4.9) but was not further attenuated with adjustment for serum creatinine and urinary albumin/creatinine ratio ($OR=2.6$, 95% CI 1.3-5.3). Results were similar for CAC extent. Conclusions: HDP may increase a woman's risk of future CHD beyond traditional risk factors and renal function. Women with a history of HDP should be monitored for potential increased risk of CHD as they age.

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Biostatistics & Research Epidemiology

Divine, G., A. Kapke, S. Havstad and C. L. Joseph (2009). "Exemplary data set sample size calculation for Wilcoxon-Mann-Whitney tests." Stat Med **EPub Ahead of Print**. [PDF Full-Text](#)

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Zhao, Rahardja and Qu consider sample size calculation for Wilcoxon-Mann-Whitney (WMW) tests for data with ties, and present a straightforward formula. We observe that the 'exemplary data set' approach, usually applied in more complex situations, has a close relationship to the Zhao-Rahardja-Qu method for WMW sample size estimation and they are asymptotically equivalent. Therefore, the exemplary data set approach can be used to easily obtain estimates similar to those that the closed formula gives. We illustrate application of both methods for a WMW sample size estimation example, and also extend the simulation study presented by Zhao et al. We find that the Zhao-Rahardja-Qu formula (and by extension the exemplary data set method) can give estimates just as accurate as those obtained using either the Kolassa approach (via nQuery Advisor) or the O'Brien-Castelloe approach (via SAS 9.2 PROC POWER), for 1:1 and 1:2 allocation ratios. However, the latter two methods can be more accurate for a ratio of 1:4 or 1:19. Finally, we note the general utility of the exemplary data set approach for sample size estimation, even in other situations where closed-form sample size formulae exist. Copyright (c) 2009 John Wiley & Sons, Ltd.

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Biostatistics & Research Epidemiology

Nock, N. L., C. Bock, C. Neslund-Dudas, J. Beebe-Dimmer, A. Rundle, D. L. Tang, M. Jankowski and B. A. Rybicki (2009). "Polymorphisms in glutathione S-transferase genes increase risk of prostate cancer biochemical recurrence differentially by ethnicity and disease severity." Cancer Causes & Control **20**(10): 1915-1926. [PDF Full-Text](#)

[Neslund-Dudas, Christine; Jankowski, Michelle; Rybicki, Benjamin A.] Henry Ford Hlth Syst, Dept Biostat & Epidemiol, Detroit, MI 48202 USA. [Nock, Nora L.] Case Western Reserve Univ, Dept Epidemiol & Biostat, Cleveland, OH 44106 USA. [Nock, Nora L.] Case Western Reserve Univ, Ctr Transdisciplinary Res Energet & Canc, Cleveland, OH 44106 USA. [Bock, Cathryn; Beebe-Dimmer, Jennifer] Wayne State Univ, Karmanos Canc Inst, Detroit, MI USA. [Rundle, Andrew; Tang, Deliang] Columbia Univ, Dept Environm Hlth Sci, New York, NY USA.

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Genetic polymorphisms that modify the detoxifying activity of glutathione S-transferases (GSTs) can affect the level of carcinogenic metabolites created by endogenous steroid hormones and exogenous chemical substances. Although the GSTM1 null genotype has been shown to increase prostate cancer mortality in Caucasians, potential associations between GST polymorphisms and prostate cancer biochemical recurrence (BCR) have not been well studied, particularly in African-Americans. We examined potential associations

between the GSTM1 null, GSTT1 null and GSTP1 Ile105Val polymorphisms and BCR, after prostatectomy, in 168 African-American and 226 Caucasian patients treated at Henry Ford Hospital in Detroit, Michigan using Cox proportional hazards modeling. We found that African-Americans with the GSTT1 null genotype had increased BCR risk compared to those having GSTT1 present (hazard ratio (HR) = 2.30; 95% CI = 1.01-5.18; $p = 0.04$); and African-Americans with the GSTT1 null genotype and high grade tumors had an even greater risk (HR = 7.82; 95% CI = 2.49-24.50; $p < 0.001$). In Caucasians, an increased risk was observed in those patients with high grade tumors and the GSTM1 null genotype (HR = 2.88; 95% CI = 1.16-7.14; $p = 0.02$). Similar associations were observed for advanced stage and more aggressive (high grade or advanced stage) disease. Our results suggest GSTs may hold promise as therapeutic targets in more advanced prostate cancers, particularly, in African-Americans.

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Biostatistics & Research Epidemiology

Ownby, D. R., M. E. Partridge, G. R. Wegienka, K. J. Woodcroft, E. L. Peterson, C. L. M. Joseph, L. K. Williams and C. C. Johnson (2009). "Influence of dose and frequency of antigen injection on IgE development in young children: a comparison of fire ant stings and tetanus immunizations." *Annals of Allergy Asthma & Immunology* 103(4): 337-341. [Article Request Form](#)

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Ownby, DR, Med Coll Georgia, Dept Allergy & Immunol, 1120 15th St, BG 1019, Augusta, GA 30912 USA. downby@mcg.edu

Background: Previous studies suggest that small antigen doses given frequently are more likely to induce IgE production than are large antigen doses given infrequently. Objective: To compare the prevalence of antitetanus IgE resulting from the relatively large dose of tetanus toxoid delivered by standard immunizations at 2, 4, 6, and 18 months of age with the previously reported prevalence of anti-fire ant venom IgE resulting from the relatively small dose of venom delivered sporadically by accidental fire ant stings in children younger than 5 years. Methods: This study uses previously published data on the prevalence of IgE antibodies to imported fire ant venom among children living in an imported fire ant endemic area of Georgia and antitetanus IgE measurements of children recruited between August 1, 2003, and December 30, 2007, as part of the Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study in Michigan, where there are no imported fire ants. The prevalence of anti-fire ant venom IgE antibodies was compared with the prevalence of antitetanus I-E antibodies in these 2 cohorts of children. Results: The reported prevalence of IgE to fire ant venom among 42 children 2 to 5 years old was 57.1% using a cutoff of 0.1 IU/mL and 35.7% using a cutoff of 0.35 IU/mL. The prevalence of antitetanus IgE in 395 children 2 years old was 52.9% using a cutoff of 0.1 IU/mL and 42.7% using a cutoff of 0.35 IU/mL. The proportion of children with detectable anti-fire ant venom IgE was not statistically significantly different from the proportion of those with antitetanus IgE at either cutoff level ($P = .74$ and $.50$ at 0.1 and 0.35 IU/mL, respectively). Conclusions: The relatively large dose of tetanus toxoid delivered 4 times during the first 24 months of life produces detectable tetanus specific IgE antibodies as frequently as the smaller doses of venom delivered sporadically by fire ant stings in young children. *Ann Allergy Asthma Immunol.* 2009; 103:337-341.

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Biostatistics & Research Epidemiology

Perry, L. M., D. R. Ownby, G. R. Wegienka, E. L. Peterson, K. J. Woodcroft, C. L. Joseph and C. C. Johnson (2009). "Differences in total and allergen specific IgE during pregnancy compared with 1 month and 1 year post partum." *Annals of Allergy Asthma & Immunology* 103(4): 342-347. [PDF Full-Text](#)

[Perry, Lee M.; Ownby, Dennis R.] Med Coll Georgia, Sect Allergy & Immunol, Augusta, GA 30912 USA. [Wegienka, Ganesa R.; Peterson, Edward L.; Woodcroft, Kimberly J.; Joseph, Christine L.; Johnson, Christine C.] Henry Ford Hosp, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA.

Ownby, DR, Med Coll Georgia, Sect Allergy & Immunol, 1120 15th St, BG 1019, Augusta, GA 30912 USA. downby@mcg.edu

Background: Pregnancy alters the function of many body systems, including the immune system. However, little is known regarding the effect of pregnancy on maternal IgE levels or atopy. Objective: To determine whether pregnancy consistently influences serum levels of total or allergen specific: IgE. Methods: Blood samples were obtained from 764 women during the third trimester of pregnancy and 1 month post partum. A third sample was obtained from 106 of these women 1 year post partum. Samples were analyzed for total and specific IgE to 8 regionally common allergens using a commercially available system. Sensitization was defined as an allergen specific IgE level of 0.35 W of allergen per liter or higher to any allergen. Results: Total IgE increased significantly post partum, both at 1 month (40.36 vs 35.37 IU/mL intrapartum; $P = .001$) and at 1 year (44.97 vs 37.00 IU/mL intrapartum; $P = .005$). Allergen specific IgE decreased significantly at 1 month for cat, dog, ragweed, timothy grass, and egg ($P = .001$ to $P = .02$) but not for dust mite, cockroach, or *Alternaria* ($P = .15$ to $P = .90$). Similar patterns of change in total and specific IgE were seen at 1 year. However, on average, only 3.5% of participants changed sensitization status to the individual allergens studied during the 1 year of observation. Conclusions: Compared with intrapartum levels, total IgE levels increased significantly at 1 month and 1 year post partum. Conversely, at the same time points, IgE levels specific for common allergens significantly declined to most but not all allergens. Few women changed their sensitization status over 1 year. *Ann Allergy Asthma Immunol.* 2009; 103:342-347.

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Biostatistics & Research Epidemiology

Yood, M. U., F. Wang, Z. Zhao, S. H. Alford, S. Oliveria, K. Wells, S. Phillips, H. Ali, C. O'Malley and B. Barber (2009). "Treatment-Related Toxicities in Patients with Squamous Cell Carcinoma of the Head and Neck (Scchn)." *Value in Health* 12(7): A225-A225. [PDF Full-Text](#) (Scroll down to page A225)

[Yood, M. U.; Oliveria, S.; Phillips, S.] Epi Source, Hamden, CT USA. [Wang, F.; Zhao, Z.; O'Malley, C.; Barber, B.] Amgen Inc, Thousand Oaks, CA 91320 USA. [Alford, S. H.; Wells, K.] Henry Ford Hlth Syst, Detroit, MI USA.

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Bone & Joint Center

Bey, M. J., S. K. Kline, R. Zael, P. A. Kolowich and T. R. Lock "In Vivo Measurement of Glenohumeral Joint Contact Patterns." *Eurasip Journal on Advances in Signal Processing*. [Article Request Form](#)

[Bey, Michael J.; Kline, Stephanie K.; Zael, Roger; Kolowich, Patricia A.; Lock, Terrence R.] Henry Ford Hosp, Dept Orthopaed Surg, Ctr Bone & Joint, Detroit, MI 48202 USA.

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The objectives of this study were to describe a technique for measuring in-vivo glenohumeral joint contact patterns during dynamic activities and to demonstrate application of this technique. The experimental technique calculated joint contact patterns by combining CT-based 3D bone models with joint motion data that were accurately measured from biplane x-ray images. Joint contact patterns were calculated for the repaired and contralateral shoulders of 20 patients who had undergone rotator cuff repair. Significant differences in joint contact patterns were detected due to abduction angle and shoulder condition (i.e., repaired versus contralateral). Abduction angle had a significant effect on the superior/inferior contact center position, with the average joint contact center of the repaired shoulder 12.1% higher on the glenoid than the contralateral shoulder. This technique provides clinically relevant information by calculating in-vivo joint contact patterns during dynamic conditions and overcomes many limitations associated with conventional techniques for quantifying joint mechanics.

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Bone & Joint Center

Ciarelli, T. E., C. Tjhia, D. S. Rao, S. J. Qiu, A. M. Parfitt and D. P. Fyhrie (2009). "Trabecular packet-level lamellar density patterns differ by fracture status and bone formation rate in white females." *Bone* 45(5): 903-908. [PDF Full-Text](#)

[Tjhia, Crystal; Fyhrie, David P.] Univ Calif Davis, Med Ctr, Lawrence J Ellison Musculoskeletal Res Ctr, Sacramento, CA 95817 USA. [Ciarelli, Traci E.] Henry Ford Hosp, Dept Orthopaed Surg, Ctr Bone & Joint, Detroit, MI 48202 USA. [Rao, D. Sudhaker; Qiu, Shijing] Henry Ford Hosp, Bone & Mineral Res Lab, Detroit, MI 48202 USA. [Parfitt, A. Michael] Univ Arkansas Med Sci, Div Endocrinol, Little Rock, AR 72205 USA. [Parfitt, A. Michael] Univ Arkansas Med Sci, Ctr Osteoporosis & Metab Bone Dis, Little Rock, AR 72205 USA. Fyhrie, DP, Univ Calif Davis, Med Ctr, Lawrence J Ellison Musculoskeletal Res Ctr, Res Bldg 1, Room 2000, 4635 2nd Ave, Sacramento, CA 95817 USA. dpfyhrie@ucdavis.edu

Spatial patterns of mineralization for human iliac crest cancellous bone were measured from images obtained by quantitative backscattered electron microscopy. Biopsies collected from vertebral fracture patients and healthy individuals with high or low bone formation rate (BFRs) were examined (fracture/low BFRs: N = 12, fracture/high BFRs: N = 10, normal/low BFRs: N = 12, normal/high BFRs: N = 15). 20 by 20 pixel square areas or smaller were sampled from superficial and deep remodeling packets. Mean (Z(mean)) and standard deviation (SD) of mineralization were measured, and coefficients of variation (CV=SD/Z(mean)) were calculated. Fast Fourier transform analysis was used to quantify the distribution of the mineral in the packets. "FFT_ratio" was defined as the ratio magnitude of the principal spatial frequency to the average atomic number density. A higher FFT_ratio occurred in specimens with more pronounced alternating layers of light and dark as visible in the backscattered electron image, which was defined as lamellar patterning. Two-way ANOVA revealed that the coefficients of variation of mineralization for both superficial and deep packets were significantly lower in fracture patients than in normal individuals. However, the interaction between turnover rate and group (fracture/non-fracture) indicated that the difference in packet CV occurred among the low turnover individuals and not among those with high turnover. Mean mineralization levels and CV between deep and superficial packets were highly correlated. Regressions of packet CV of mineralization and FFT_ratio were highly significant ($p < 0.001$) for all packets pooled and for packets divided by group (fracture/normal). However, analyses of packet CV and FFT_ratio by individual were variable (R^2 from 0.00338 to 0.700). Packet-level mineralization variability may be associated with fracture toughness, and fracture patients had less variable packet-level mineralization. The result that the packet CV varied significantly between fracture and non-fracture individuals with low turnover suggests that for low turnover subjects without fracture, high variability in mineralization may have a protective effect. In high turnover patients, the accelerated turnover may prevent the lamellar variability from developing over time. Strong correlations between CV and Z(mean) for both superficial and deep packets imply that newly formed bone is created similarly to older bone within an individual. Fourier transform results show that the mineralization variability found within packets is associated with lamellar patterning. Lamellar structure has been hypothesized to guide microcrack propagation in order to optimize bone strength and toughness. Osteoporotics with fracture had less pronounced lamellation than healthy normals and may be more prone to fracture. (C) 2009 Elsevier Inc. All rights reserved.

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Bone & Joint Center

Yeni, Y. N., X. N. Dong, B. B. Zhang, G. J. Gibson and D. P. Fyhrie (2009). "Cancellous Bone Properties and Matrix Content of TGF-beta 2 and IGF-I in Human Tibia: A Pilot Study." Clinical Orthopaedics and Related Research **467**(12): 3079-3086. [PDF Full-Text](#)

[Yeni, Yener N.] Henry Ford Hosp, Dept Orthopaed & Rehabil, Sect Biomech, Ctr Bone & Joint, Detroit, MI 48202 USA. [Dong, X. Neil] Univ Texas San Antonio, Dept Mech Engr, San Antonio, TX USA. [Zhang, Bingbing; Gibson, Gary J.] Henry Ford Hosp, Sect Cell Biol, Dept Orthopaed & Rehabil, Ctr Bone & Joint, Detroit, MI 48202 USA. [Fyhrie, David P.] Univ Calif Davis, Dept Orthopaed Surg, Lawrence J Ellison Musculoskeletal Res Ctr, Sacramento, CA 95817 USA.

Yeni, YN, Henry Ford Hosp, Dept Orthopaed & Rehabil, Sect Biomech, Ctr Bone & Joint, 2799 W Grand Blvd, E&R 2015, Detroit, MI 48202 USA. yeni@bjc.hfh.edu

Transforming and insulin-like growth factors are important in regulating bone mass. Thus, one would anticipate correlations between matrix concentrations of growth factors and functional properties of bone. We therefore investigated the relationships of (1) TGF-beta 2 and (2) IGF-I matrix concentrations with the trabecular microstructure, stress distribution, and mechanical properties of tibial cancellous bone from six male human cadavers. Trabecular stress amplification (VMExp/sigma(app)) and variability (VMCOV) were calculated using microcomputed tomography (mu CT)-based finite element simulations. Bone volume fraction (BV/TV), surface/volume ratio (BS/BV), trabecular thickness (Tb.Th), number (Tb.N) and separation (Tb.Sp), connectivity (Eu.N), and anisotropy (DA) were measured using 3-D morphometry. Bone stiffness and strength were measured by mechanical testing. Matrix concentrations of TGF-beta 2 and IGF-I were measured by ELISA. We found higher matrix concentrations of TGF-beta 2 were associated with higher Tb.Sp and VMExp/sigma(app) for pooled data and within subjects. Similarly, a higher matrix concentration of IGF-I was

associated with lower stiffness, strength, BV/TV and Tb.Th and with higher BS/BV, Tb.Sp, VMExp/sigma(app) and VMCOV for pooled data and within subjects. IGF-I and Tb.N were negatively associated within subjects. It appears variations of the stress distribution in cancellous bone correlate with the variation of the concentrations of TGF-beta 2 and IGF-I in bone matrix: increased local matrix concentrations of growth factors are associated with poor biomechanical and architectural properties of tibial cancellous bone.

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Bone & Joint Center

Yerramshetty, J., D. G. Kim and Y. N. Yeni (2009). "Increased Microstructural Variability is Associated With Decreased Structural Strength But With Increased Measures of Structural Ductility in Human Vertebrae." Journal of Biomechanical Engineering-Transactions of the Asme **131**(9). [Article Request Form](#)

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The lack of accuracy in the prediction of vertebral fracture risk from average density measurements, all external factors being equal, may not just be because bone mineral density (BMD) is less than a perfect surrogate for bone strength but also because strength alone may not be sufficient to fully characterize the structural failure of a vertebra. Apart from bone quantity, the regional variation (if cancellous architecture would have a role in governing the mechanical properties of vertebrae. In this study, we estimated various microstructural parameters of the vertebral cancellous centrum based on stereological analysis. An earlier study, indicated that within-vertebra variability, measured as the coefficient of variation (COV) of bone volume fraction (BV/TV) or as COV of finite element-estimated apparent modulus (EFE) correlated well with vertebral strength. Therefore, as an extension to our earlier study, we investigated (i) whether the relationships of vertebral strength found with COV of BV/TV and COV of E-FE could be extended to the COV of other microstructural parameters and microcomputed tomography-estimated BMD and (ii) whether COV of microstructural parameters were associated with structural ductility measures. COV-based measures were more strongly associated with vertebral strength and ductility measures than average microstructural measures. Moreover, our results support a hypothesis that decreased microstructural variability, while associated with increased strength, may result in decreased structural toughness and ductility. The current findings suggest that variability-based measures could provide an improvement, as a supplement to clinical BMD, in screening for fracture risk through an improved prediction of bone strength and ductility. Further understanding of the biological mechanisms underlying microstructural variability may help develop new treatment strategies for improved structural ductility. [DOI: 10.1115/1.3148473]

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Cardiology

Atchley, A. E., D. W. Kitzman, D. J. Whellan, A. E. Iskandrian, S. J. Ellis, L. K. Shaw, R. A. Pagnanelli, A. Kao, K. Abdul-Nour, G. Ewald, C. M. O'Connor, W. E. Kraus and S. Borges-Neto (2009). "Relationship of Baseline Gated Rest SPECT Myocardial Perfusion Imaging to Death and Hospitalization in Heart Failure Patients: Results from the Nuclear Substudy of the HF-ACTION Trial." Journal of Cardiac Failure **15**(9): 814-814. [PDF Full-Text](#)

[Atchley, Allen E.; Ellis, Stephen J.; Shaw, Linda K.; Pagnanelli, Robert A.; O'Connor, Christopher M.; Kraus, William E.; Borges-Neto, Salvador] Duke Univ, Med Ctr, Durham, NC USA. [Kitzman, Dalane W.] Wake Forest Univ, Winston Salem, NC 27109 USA. [Whellan, David J.] Thomas Jefferson Univ, Jefferson Med Coll, Philadelphia, PA 19107 USA. [Iskandrian, Ami E.] Univ Alabama, Birmingham, AL USA. [Kao, Andrew] St Lukes Hosp, Mid Amer Heart Inst, Kansas City, MO 64111 USA. [Abdul-Nour, Khaled] Henry Ford Hosp, Detroit, MI 48202 USA. [Ewald, Greg] Washington Univ, St Louis, MO USA.

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Cardiology

Khan, H., M. Metra, J. E. A. Blair, M. Vogel, M. E. Harinstein, G. S. Filippatos, H. N. Sabbah, H. Porchet, G. Valentini and M. Gheorghiuade (2009). "Istaroxime, a first in class new chemical entity exhibiting SERCA-2 activation and Na-K-ATPase inhibition: a new promising

treatment for acute heart failure syndromes?" [Heart Failure Reviews](#) **14**(4): 277-287. [PDF Full-Text](#)

[Gheorghide, Mihai] Northwestern Univ, Feinberg Sch Med, Div Cardiol, Chicago, IL 60611 USA. [Metra, Marco] Univ Brescia, Dept Cardiol, Brescia, Italy. [Filippatos, Gerasimos S.] Univ Hosp Attikon, Athens, Greece. [Sabbah, Hani N.] Henry Ford Hosp, Detroit, MI 48202 USA. [Porchet, Herve] Debiopharm SA, Lausanne, Switzerland. [Valentini, Giovanni] Sigma Tau Ifr SpA, Rome, Italy.
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Acute heart failure syndromes (AHFS) are associated with the rapid onset of heart failure (HF) signs and symptoms. Hospitalizations for AHFS continue to rise and are associated with significant mortality and morbidity. Several pharmacological agents are currently approved for the treatment of AHFS, but their use is associated with an increase in short-term mortality. There is a need for new agents that can be given in the acute setting with increased efficacy and safety. Istaroxime is a unique agent with both inotropic and lusitropic properties which is currently being studied for the treatment of AHFS. Istaroxime inhibits the sodium-potassium adenosine triphosphatase (ATPase) and stimulates the sarcoplasmic reticulum calcium ATPase isoform 2 (SERCA-2) thereby improving contractility and diastolic relaxation. Early data from human studies reveal that istaroxime decreases pulmonary capillary wedge pressure (PCWP) and possibly improves diastolic function without causing a significant change in heart rate (HR), blood pressure, ischemic or arrhythmic events. Most commonly reported side effects were related to gastrointestinal intolerance and were dose related. In conclusion, istaroxime is a novel agent being investigated for the treatment of AHFS whose mechanism of action and cellular targets make it a promising therapy. Further studies with longer infusion times in patients with hypotension are required to confirm its efficacy and safety.

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Cardiology

Teerlink, J. R., M. Metra, V. Zaca, H. N. Sabbah, G. Cotter, M. Gheorghide and L. Dei Cas (2009). "Agents with inotropic properties for the management of acute heart failure syndromes. Traditional agents and beyond." [Heart Failure Reviews](#) **14**(4): 243-253. [PDF Full-Text](#)

[Metra, Marco; Dei Cas, Livio] Univ Brescia, Spedali Civili Brescia, Dept Expt & Appl Med, I-25123 Brescia, Italy. [Teerlink, John R.] Univ Calif San Francisco, San Francisco Vet Affairs Med Ctr, Cardiol Sect, San Francisco, CA 94143 USA. [Zaca, Valerio] Santa Maria Scotte Hosp, Div Cardiol, Cardiovasc & Thorac Dept, Siena, Italy. [Sabbah, Hani N.] Henry Ford Hosp, Henry Ford Heart & Vasc Inst, Div Cardiovasc Med, Dept Med, Detroit, MI 48202 USA. [Cotter, Gadi] Momentum Res, Durham, NC USA. [Gheorghide, Mihai] Northwestern Univ, Feinberg Sch Med, Chicago, IL 60611 USA.
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Treatment with inotropic agents is one of the most controversial topics in heart failure. Initial enthusiasm, based on strong pathophysiological rationale and apparent empirical efficacy, has been progressively limited by results of controlled trials and registries showing poorer outcomes of the patients on inotropic therapy. The use of these agents remains, however, potentially indicated in a significant proportion of patients with low cardiac output, peripheral hypoperfusion and end-organ dysfunction caused by heart failure. Limitations of inotropic therapy seem to be mainly related to their mechanisms of action entailing arrhythmogenesis, peripheral vasodilation, myocardial ischemia and damage, and possibly due to their use in patients without a clear indication, rather than to the general principle of inotropic therapy itself. This review will discuss the characteristics of the patients with a potential indication for inotropic therapy, the main data from registries and controlled trials, the mechanism of the untoward effects of these agents on outcomes and, lastly, perspectives with new agents with novel mechanisms of action.

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Dermatology

Hood, A. F. (2009). "Dermatopathology calendar." [Journal of Cutaneous Pathology](#) **36**(12): 1330-1330. [PDF Full-Text](#)

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Dermatology

Tierney, E. and D. J. Kouba (2009). "A Subcutaneous Corset Plication Rapidly and Effectively Relieves Tension on Large Linear Closures." *Dermatologic Surgery* **35**(11): 1806-1808. [PDF Full-Text](#)

[Tierney, Emily; Kouba, David J.] Henry Ford Hlth Syst, Dept Dermatol, Detroit, MI USA.
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Diagnostic Radiology

Jain, R., L. M. Scarpace, S. Ellika, R. Torcuator, L. R. Schultz, D. Hearshen and T. Mikkelsen (2009). "Imaging response criteria for recurrent gliomas treated with bevacizumab: Role of diffusion weighted imaging as an imaging biomarker." *J Neurooncol* **Epub Ahead of Print**. [PDF Full-Text](#)

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The purpose of this study was to assess the usefulness of diffusion weighted imaging as an additional imaging biomarker for treatment response in recurrent/progressive malignant gliomas treated with bevacizumab alone or in combination with other chemotherapeutic agents. Twenty patients treated with bevacizumab alone or concurrent chemotherapy were followed up with serial MR imaging. Volume and ADC values of contrast enhancing lesion (CEL(vol), CEL(ADC)) and also of non-enhancing lesion (NEL(vol), NEL(ADC)) were obtained. CEL(vol) showed a progressive decrease in non-progressors with a median percentage change of -73.2% (P = 0.001) as compared to -33.4% for progressors by 1 year/last imaging (P = 0.382). NEL(vol) also showed a decrease in non-progressors on follow up imaging though only significant for 3 months follow up (P = 0.042). In progressors, CEL(vol) and NEL(vol) showed initial decrease followed by slight increase by 1 year/last imaging though not significant (P value of 0.382 and 0.46, respectively). CEL(ADC) and NEL(ADC) in non-progressors did not show any statistically significant change though there was slight trend for positive percent change especially for CEL(ADC) by 1 year/last imaging follow up study (P value of 0.077 and 0.339, respectively). Progressors showed a progressive negative percent change of CEL(ADC) and NEL(ADC). In progressors, NEL(ADC) decreased at 6 weeks (P = 0.054), 3 months (P = 0.023) and 1 year/last (P = 0.078) as compared to baseline study and was also statistically significant as compared to non-progressors at 6 weeks (P = 0.047) and 3 months (P = 0.025). CEL(ADC) and NEL(ADC) appear to follow different trends over time for non-progressors and progressors with a stable to slightly progressive increase in non-progressors and a progressive decrease in progressors, especially early on. These findings suggest that DWI may be used as an additional imaging biomarker for early treatment response.

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Diagnostic Radiology

Shalchian, B., H. Rajabi and H. Soltanian-Zadeh (2009). "Assessment of the Wavelet Transform in Reduction of Noise from Simulated PET Images." *J Nucl Med Technol* **37**(4): 223-8. [Article Request Form](#)

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An efficient method for tomographic imaging in nuclear medicine is PET. Higher sensitivity, higher spatial resolution, and more accurate quantification are advantages of PET, in comparison to SPECT. However, a high noise level in the images limits the diagnostic utility of PET. Noise removal in nuclear medicine is traditionally based on the Fourier decomposition of the images. This method is based on frequency components, irrespective of the spatial location of the noise or signal. The wavelet transform presents a solution by providing information on frequency contents while retaining spatial information, alleviating the

shortcoming of Fourier transformation. Thus, wavelet transformation has been extensively used for noise reduction, edge detection, and compression. METHODS: In this research, SimSET software was used for simulation of PET images of the nonuniform rational B-spline-based cardiac-torso phantom. The images were acquired using 250 million counts in 128 x 128 matrices. For a reference image, we acquired an image with high counts (6 billion). Then, we reconstructed these images using our own software developed in a commercially available program. After image reconstruction, a 250-million-count image (noisy image or test image) and a reference image were normalized, and then root mean square error was used to compare the images. Next, we wrote and applied denoising programs. These programs were based on using 54 different wavelets and 4 methods. Denoised images were compared with the reference image using root mean square error. RESULTS: Our results indicate stationary wavelet transformation and global thresholding are more efficient at noise reduction than are other methods that we investigated. CONCLUSION: Wavelet transformation is a useful method for denoising simulated PET images. Noise reduction using this transform and loss of high-frequency information are simultaneous with each other. It seems we should attend to mutual agreement between noise reduction and visual quality of the image.

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Diagnostic Radiology

Tagliafico, A., E. Resmini, M. T. van Holsbeeck, L. E. Derchi, D. Ferone and C. Martinoli (2009). "Sonographic Depiction of Trigger Fingers in Acromegaly." Journal of Ultrasound in Medicine **28**(11): 1441-1446. [PDF Full-Text](#)

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Objective. The purpose of this study was to compare the prevalence of trigger fingers in patients with acromegaly versus an unaffected control group. Methods. This study was performed with Institutional Review Board approval, and informed written consent was obtained from each patient and control participant. The diagnosis was made by a combination of clinical symptoms and sonographically measured thickening of the first annular (A1) pulley. The A1 pulley thickness was measured in 40 patients and 40 control participants by means of a 17-5 MHz high-resolution transducer. Thickening of the A1 pulley and abnormalities of the underlying flexor tendons associated with the clinical sign were diagnostic for a trigger finger. The acromegalic patients were divided into groups according to disease activity and therapy. The study was performed at the baseline and at a follow-up after 1 year. Results. At the baseline, clinical and sonographic findings were consistent with trigger fingers in 25% of patients (6 at presentation and 4 with uncontrolled disease). After 1 year, the trigger fingers recovered in the patients who were not receiving any treatment at the beginning of the study. In patients with uncontrolled disease, the condition remained unchanged. The A1 pulley thickness was greater in the acromegalic patients than control participants (mean +/- SD, 0.44 +/- 0.19 versus 0.24 +/- 0.05 mm; P <.05). In the patients treated for acromegaly, the trigger fingers disappeared, and a reduction in the A1 pulley thickness was noted (P <.05) at the follow-up. Conclusions. Trigger fingers were observed in 25% of the acromegalic patients but in none of the control participants. The A1 pulley was significantly thicker in the acromegalic patients and normalized after 1 year in some who were treated for the disease.

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Emergency Medicine

Boehm, K. M., E. Yum and T. Caraccio (2009). "An overdose of aconite by a twenty-six-year-old woman." J Emerg Med. [PDF Full-Text](#)

Department of Emergency Medicine, Henry Ford Wyandotte Hospital, Wyandotte, Michigan, Long Island Regional Poison & Drug Information Center (LIRPDIC), Winthrop-University Hospital, Mineola, New York.

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Emergency Medicine

Rivers, E. P., V. Coba and M. Rudis (2009). "Standardized order sets for the treatment of severe sepsis and septic shock." Expert Rev Anti Infect Ther 7(9): 1075-9. [Article Request Form](#)

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Evaluation of: Thiel SW, Asghar MF, Micek ST, Reichley RM, Doherty JA, Kollef MH. Hospital-wide impact of standardized order set for the management of bacteremic severe sepsis. *Crit. Care Med.* 37(3), 819-824 (2009). Aggressive standardized diagnostic and therapeutic approaches to acute diseases such as acute myocardial infarction, trauma and stroke have led to improved patient survival. A standardized order set for severe sepsis and septic shock represents a similar approach. In 2001, Rivers et al., using a standardized operating procedure to treat severe sepsis and septic shock, showed a relative risk reduction of 0.34 and absolute risk reduction of 16%, with a decrease in healthcare resource consumption for patients presenting to the emergency department. Since then, similar studies have shown similar or better results. This study in particular highlights a hospital-wide initiative that further confirms that standardized order sets and operating procedures for severe sepsis and septic shock result in a significant reduction in morbidity, mortality and healthcare resource consumption. With these robust findings, future emphasis should be placed on overcoming logistical, institutional and professional barriers to the implementation of standardized order sets, which can save the life of one out of every five to six patients presenting with severe sepsis and septic shock.

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Endocrinology & Metabolism

Wang, X. Q., S. J. Qiu, X. Yao, T. T. Tang, K. R. Dai and Z. A. Zhu (2009). "Berberine Inhibits Staphylococcus Epidermidis Adhesion and Biofilm Formation on the Surface of Titanium Alloy." Journal of Orthopaedic Research 27(11): 1487-1492. [PDF Full-Text](#)

[Wang, Xiaoqing; Tang, Tingting; Dai, Kerong; Zhu, Zhen'an] Shanghai Jiao Tong Univ, Dept Orthopaed Surg, Peoples Hosp 9, Sch Med, Shanghai 200011, Peoples R China. [Qiu, Shijing] Henry Ford Hosp, Bone & Mineral Res Lab, Detroit, MI 48202 USA. [Yao, Xiao] Shanghai Jiao Tong Univ, State Key Lab Oncogenes & Related Genes, Shanghai Canc Inst, Shanghai 200032, Peoples R China. Zhu, ZA, Shanghai Jiao Tong Univ, Dept Orthopaed Surg, Peoples Hosp 9, Sch Med, Shanghai 200011, Peoples R China. zhuzhenan@sjtu.edu.cn

Biofilm formed by Staphylococcus epidermidis (*S. epidermidis*) is a common cause of periprosthetic infection. Recently, we have discovered that berberine is bacteriostatic for *S. epidermidis*. The purpose of the present study was to examine the effect of berberine on *S. epidermidis* adhesion and biofilm formation on the surface of titanium alloy, which is a popular material for orthopedic joint prostheses. Three strains of *S. epidermidis* (ATCC 35984, ATCC 12228, and SE 243) were used for in vitro experiment. Direct colony counting showed that berberine significantly inhibited *S. epidermidis* adhesion on the titanium alloy disk in 2 h at the concentration of 45 $\mu\text{g/mL}$. When examined with crystal violet staining, confocal laser scanning microscopy, and scanning electron microscopy, we found that higher concentrations ($>30 \mu\text{g/mL}$) of berberine effectively prevented the formation of *S. epidermidis* biofilm on the surface of the titanium disk in 24 h. These findings suggest that berberine is a potential agent for the treatment of periprosthetic infection. (C) 2009 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. *J Orthop Res* 27:1487-1492, 2009

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Family Medicine

Wagner, J. A., D. W. Perkins, J. D. Piette, B. Lipton and J. E. Aikens (2009). "Racial differences in the discussion and treatment of depressive symptoms accompanying type 2 diabetes." Diabetes Research and Clinical Practice 86(2): 111-116. [Article Request Form](#)

[Wagner, Julie A.] Univ Connecticut, Ctr Hlth, Farmington, CT 06030 USA. [Perkins, Denise White] Henry Ford Hlth Syst, Inst Multicultural Hlth, Detroit, MI USA. [Piette, John D.] Univ Michigan, Dept Internal Med, Ann Arbor, MI 48109 USA. [Piette, John D.] Univ Michigan, Diabet Res & Training Ctr, Ann Arbor, MI 48109 USA. [Piette, John D.; Aikens, James E.] Dept Vet Affairs Med Ctr, Hlth Serv Res & Dev Ctr Excellence, Ann Arbor, MI USA. [Lipton, Bonnie] Brigham & Womens Hosp, Orthoped & Arthrit Ctr Outcomes Res, Boston, MA 02115 USA. [Aikens, James E.] Univ Michigan, Dept Family Med, Ann Arbor, MI 48109 USA.

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Objective: To compare rates of discussion of and treatment for depression among African Americans and Whites with diabetes. Methods: Measures of diabetes status, depressive symptoms, and history of discussing and being treated for depression were collected from 56 adults with elevated depressive symptoms accompanying diabetes who were drawn from a larger study of type 2 diabetes. Results: Analyses adjusted for confounders and multiple tests indicated that relative to Whites, African Americans were 6-12 times less likely to have ever: discussed depression with anyone ($p = .007$), discussed depression with their primary care physician ($p = .008$), been prescribed an antidepressant ($p = .002$), and they were 25 times less likely to have seen a psychiatrist ($p = .003$). There were no significant differences in discussing depression with clergypersons, or family members/friends. Conclusions: Compared to their White counterparts, African Americans with depressive symptoms accompanying diabetes are unlikely to discuss depression with healthcare professionals, be prescribed antidepressant medication, or be seen by a psychiatrist. Minority diabetes patients' medical and psychiatric outcomes may improve if healthcare providers more actively initiate these discussions, provide culturally tailored education about the nature of depression and its management, incorporate patient preferences into treatment plans, and establish relationships with persons more likely to learn about African American patient symptoms. (C) 2009 Elsevier Ireland Ltd. All rights reserved.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Kaseb, A. O., A. Hanbali, M. Cotant, M. M. Hassan, I. Wollner and P. A. Philip (2009). "Vascular Endothelial Growth Factor in the Management of Hepatocellular Carcinoma A Review of Literature." *Cancer* **115**(21): 4895-4906. [PDF Full-Text](#)

[Philip, Philip A.] Wayne State Univ, Karmanos Canc Ctr, Dept Hematol Oncol, Detroit, MI 48201 USA. [Kaseb, Ahmed O.; Hassan, Manal M.] Univ Texas MD Anderson Canc Ctr, Dept Gastrointestinal Med Oncol, Houston, TX 77030 USA. [Hanbali, Amr; Wollner, Ira] Henry Ford Hosp, Dept Hematol & Oncol, Detroit, MI 48202 USA. [Cotant, Matthew] Beaumont Hosp, Dept Hematol Oncol, Royal Oak, MI USA. Philip, PA, Wayne State Univ, Karmanos Canc Ctr, Dept Hematol Oncol, 4-HWCRC,4100 John R St, Detroit, MI 48201 USA. philipp@karmanos.org

The importance of tumor angiogenesis in tumor biology is now widely accepted. Hepatocellular carcinoma (HCC) is a highly vascular tumor, and angiogenesis is believed to play a considerable role in its development and progression. The authors reviewed the role of circulating vascular endothelial growth factor (VEGF) in screening for HCC and in risk stratification and treatment monitoring. They searched the world medical literature by accessing MEDLINE and PubMed for articles on: 1) the utility of circulating VEGF for HCC screening in patients with cirrhosis; 2) the role of circulating VEGF as a predictor of the invasive potential of HCC; and 3) monitoring anti-HCC treatment effects by serial measurements of circulating VEGF. They found evidence to support a potential role for VEGF in screening and surveillance of HCC. They also found support for developing the use of VEGF in the monitoring of treatment outcomes. Several studies suggested that the circulating VEGF level may be an independent prognostic marker in HCC. Further studies are needed to determine the utility of circulating VEGF in screening of patients with cirrhosis and to determine its potential role as a prognostic and predictive biomarker in patients with HCC. *Cancer* 2009;115:4895-906. (C) 2009 American Cancer Society.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Lambing, A. and E. Kachalsky (2009). "The new age of haemophilia." *Haemophilia* **15**(6): 1330-1331. [PDF Full-Text](#)

[Lambing, A.; Kachalsky, E.] Henry Ford Hlth Syst, Hemophilia & Thrombosis Treatment Ctr, Detroit, MI 48202 USA. Lambing, A, Henry Ford Hlth Syst, Hemophilia & Thrombosis Treatment Ctr, Detroit, MI 48202 USA. alambin1@hfhs.org

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Hospitalist Medicine

Caverzagie, K. J., E. C. Bernabeo, S. G. Reddy and E. S. Holmboe (2009). "The Role of Physician Engagement Impact of the Hospital-Based Practice Improvement on the Module (PIM)." Journal of Hospital Medicine 4(8): 466-470. [PDF Full-Text](#)

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BACKGROUND: Physicians play an important role in hospital quality improvement (QI) activities. The Hospital-Based Practice Improvement Module (Hospital PIM) is a web-based assessment tool designed by the American Board of Internal Medicine (ABIM) to facilitate physician involvement in QI as a part of maintaining certification. **OBJECTIVE:** The primary objective of this study is to explore the impact of the Hospital PIM on physicians participating in hospital-based QI. **DESIGN:** Qualitative design consisting of semistructured telephone interviews. **PARTICIPANTS:** A purposeful sample of 21 early-completers of the Hospital PIM. **MEASUREMENTS:** Grounded-theory analysis was used to analyze transcripts of the semistructured telephone interviews. **RESULTS:** Physician completers of the Hospital PIM describe the impact in a variety of ways, including new learning about QI principles and activities, added value to their practice, and enhanced QI experience. An emerging theme was the mediating role of physician engagement in relation to the overall impact of the Hospital PIM. Four case studies illustrate these findings. Facilitators and barriers that influence the overall experience of the PIM are described. **CONCLUSIONS:** The impact of completing the Hospital PIM is mediated by the degree of physician engagement with the QI process. Physicians who become engaged with the Hospital PIM and QI process may be more likely to report successful experiences in implementing QI activities in hospital settings than those who do not become engaged. *Journal of Hospital Medicine* 2009;4:466-470. (C) 2009 Society of Hospital Medicine.

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Hospitalist Medicine

Green, M. L., E. M. Aagaard, K. J. Caverzagie, D. A. Chick, E. Holmboe, G. Kane, C. D. Smith and W. Iobst (2009). "Charting the road to competence: Developmental milestones for internal medicine residency training." Journal of Graduate Medical Education 1(1): 5-20. [PDF Full-Text](#)

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Hypertension & Vascular Research

Ardanaz, N., X. P. Yang, M. E. Cifuentes, M. J. Haurani, K. W. Jackson, T. D. Liao, O. A. Carretero and P. J. Pagano (2009). "Lack of Glutathione Peroxidase 1 Accelerates Cardiac-Specific Hypertrophy and Dysfunction in Angiotensin II Hypertension." Hypertension **EPub Ahead of Print**. [Article Request Form](#)

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Glutathione peroxidase 1 (Gpx1) plays an important role in cellular defense by converting hydrogen peroxide and organic hydroperoxides to nonreactive products, and Gpx1(-/-) mice, which are characterized by reduced tissue glutathione peroxidase activity, are known to exhibit enhanced oxidative stress. Peroxides participate in tissue injury, as well as the hypertrophy of cultured cells, yet the role of Gpx1 to prevent end organ damage in cardiovascular tissue is not clear. We postulated that Gpx1 deletion would potentiate both aortic and cardiac hypertrophy, as well as mean arterial blood pressure, in response to angiotensin II (AngII). Our results show that short-term AngII markedly increased left ventricular mass, myocyte cross-sectional area, and interventricular septum thickness and decreased shortening fraction in Gpx1(-/-) mice as compared with wild-type animals. On the other hand, AngII resulted in a similar increase in mean arterial blood pressure in wild-type and Gpx1(-/-) mice. Collagen deposition increased in response to AngII, but no differences were found between strains. Vascular hypertrophy increased to the same extent in Gpx1(-/-) and wild-type mice. Collectively, our results indicate that Gpx1 deficiency accelerates cardiac hypertrophy and dysfunction but has

no effect on vascular hypertrophy and mean arterial blood pressure and suggest a major role for Gpx1 in cardiac dysfunction in AngII-dependent hypertension.

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Hypertension & Vascular Research

He, Q., P. Harding and M. C. Lapointe (2009). "PKA, Rap1, ERK1/2, and p90RSK mediate PGE2 and EP4 signaling in neonatal ventricular myocytes." *Am J Physiol Heart Circ Physiol* **Epub Ahead of Print**. [PDF Full-Text](#)

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We have previously reported that: 1) inhibition of cyclooxygenase-2 and PGE2 production reduces hypertrophy following myocardial infarction in mice; and 2) PGE2 acting through its EP4 receptor causes hypertrophy of neonatal ventricular myocytes (NVM) via ERK1/2. It is known that EP4 couples to adenylate cyclase, cAMP and protein kinase A (PKA). Our present studies were designed to determine interactions between the cAMP-PKA pathway and ERK1/2 and to further characterize events downstream of ERK1/2. We hypothesized that PKA and the small GTPase Rap are upstream of ERK1/2 and that the 90 kDa ribosomal S6 kinase (p90RSK) is activated downstream. Treatment of NVM with PGE2 activated Rap and this activation was inhibited in part by an EP4 antagonist and PKA inhibition. Transfection of a dominant-negative mutant of Rap reduced PGE2 activation of ERK1/2. PGE2 activation of p90RSK was also dependent on EP4, PKA, and Rap. We also tested the involvement of Rap, ERK1/2 and p90RSK in PGE2 regulation of gene expression. PGE2 stimulation of the BNP promoter activity was blocked by either ERK1/2 inhibition or a dominant negative mutation of p90RSK. PGE2 stimulation of c-Fos was dependent on EP4, PKA, ERK1/2 and p90RSK, whereas only the latter two kinases were involved in PGE2 regulation of Egr-1. Finally, we tested the involvement of EP4-dependent signaling in the NVM growth response and found that overexpression of EP4 increased NVM cell size. We conclude that EP4-dependent signaling in NVM in part involves PKA, Rap, ERK1/2, and p90RSK and results in increased expression of BNP and c-Fos. Key words: Prostaglandins, EP4, signaling.

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Hypertension & Vascular Research

Li, X. C., U. Hopfer and J. L. Zhuo (2009). "AT1 receptor-mediated uptake of angiotensin II and NHE-3 expression in proximal tubule cells through a microtubule-dependent endocytic pathway." *Am J Physiol Renal Physiol* **297**(5): F1342-52. [PDF Full-Text](#)

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Angiotensin II (ANG II) is taken up by proximal tubule (PT) cells via AT1 (AT1a) receptor-mediated endocytosis, but the underlying cellular mechanisms remain poorly understood. The present study tested the hypothesis that the microtubule- rather than the clathrin-dependent endocytic pathway regulates AT1-mediated uptake of ANG II and ANG II-induced sodium and hydrogen exchanger-3 (NHE-3) expression in PT cells. The expression of AT1 receptors, clathrin light (LC) and heavy chain (HC) proteins, and type 1 microtubule-associated proteins (MAPs; MAP-1A and MAP-1B) in PT cells were knocked down by their respective small interfering (si) RNAs before AT1-mediated FITC-ANG II uptake and ANG II-induced NHE-3 expression were studied. AT1 siRNAs inhibited AT1 expression and blocked ANG II-induced NHE-3 expression in PT cells, as expected ($P < 0.01$). Clathrin LC or HC siRNAs knocked down their respective proteins by approximately 90% with a peak response at 24 h, and blocked the clathrin-dependent uptake of Alexa Fluor 594-transferrin ($P < 0.01$). However, neither LC nor HC siRNAs inhibited AT1-mediated uptake of FITC-ANG II or affected ANG II-induced NHE-3 expression. MAP-1A or MAP-1B siRNAs markedly knocked down MAP-1A or MAP-1B proteins in a time-dependent manner with peak inhibitions at 48 h ($>76.8\%$, $P < 0.01$). MAP protein knockdown resulted in approximately 52% decreases in AT1-mediated FITC-ANG II uptake and approximately 66% decreases in ANG II-induced NHE-3 expression ($P < 0.01$). These effects were associated with threefold decreases in ANG II-induced MAP kinases ERK 1/2 activation ($P < 0.01$), but not with altered AT1 expression or clathrin-dependent transferrin uptake. Both losartan and AT1a receptor deletion in mouse PT cells completely abolished the effects of MAP-1A knockdown on ANG II-induced NHE-3 expression and activation of MAP kinases ERK1/2. Our findings suggest that the alternative microtubule-dependent endocytic pathway, rather than the canonical clathrin-dependent pathway, plays an important role in AT1 (AT1a)-mediated uptake of extracellular ANG II and ANG II-induced NHE-3 expression in PT cells.

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Hypertension & Vascular Research

Ortiz-Capisano, M. C., T. D. Liao, P. A. Ortiz and W. H. Beierwaltes (2009). "Calcium-dependent phosphodiesterase 1C inhibits renin release from isolated juxtaglomerular cells." [American Journal of Physiology-Regulatory Integrative and Comparative Physiology](#) **297**(5): R1469-R1476. [PDF Full-Text](#)

[Ortiz-Capisano, M. Cecilia; Liao, Tang-Dong; Ortiz, Pablo A.; Beierwaltes, William H.] Henry Ford Hosp, Dept Med, Hypertens & Vasc Res Div, Detroit, MI 48202 USA.

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Ortiz-Capisano MC, Liao T-D, Ortiz PA, Beierwaltes WH. Calcium-dependent phosphodiesterase 1C inhibits renin release from isolated juxtaglomerular cells. *Am J Physiol Regul Integr Comp Physiol* 297: R1469-R1476, 2009. First published September 9, 2009; doi:10.1152/ajpregu.00121.2009. Renin release from the juxtaglomerular (JG) cell is stimulated by the second messenger cAMP and inhibited by calcium. We previously showed JG cells contain a calcium sensing receptor (CaSR), which, when stimulated, decreases cAMP formation and inhibits renin release. We hypothesize CaSR activation decreases cAMP and renin release, in part, by stimulating a calcium calmodulin-activated phosphodiesterase 1 (PDE1). We incubated our primary culture of JG cells with two selective PDE1 inhibitors [8-methoxymethyl-IBMX (8-MM-IBMX; 20 μ M) and vinpocetine (40 μ M)] and the calmodulin inhibitor W-7 (10 μ M) and measured cAMP and renin release. Stimulation of the JG cell CaSR with the calcimimetic cinacalcet (1 μ M) resulted in decreased cAMP from a basal of 1.13 \pm 0.14 to 0.69 \pm 0.08 pM/mg protein ($P < 0.001$) and in renin release from 0.89 \pm 0.16 to 0.38 \pm 0.08 μ g ANG I/ml.h(-1).mg protein(-1) ($P < 0.001$). However, the addition of 8-MM-IBMX with cinacalcet returned both cAMP (1.10 \pm 0.19 pM/mg protein) and renin (0.57 \pm 0.16 μ g ANG I/ml.h(-1).mg protein(-1)) to basal levels. Similar results were obtained with vinpocetine, and also with W-7. Combining 8-MM-IBMX and W-7 had no additive effect. To determine which PDE1 isoform is involved, we performed Western blot analysis for PDE1A, B, and C. Only Western blot analysis for PDE1C showed a characteristic band apparent at 80 kDa. Immunofluorescence showed cytoplasmic distribution of PDE1C and renin in the JG cells. In conclusion, PDE1C is expressed in isolated JG cells, and contributes to calcium's inhibitory modulation of renin release from JG cells.

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Hypertension & Vascular Research

Silva, G. B. and J. L. Garvin (2009). "Rac1 mediates NaCl-induced superoxide generation in the thick ascending limb." [Am J Physiol Renal Physiol](#) **EPub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital.

Superoxide (O_2^-) produced by NADPH oxidase regulates Na absorption and renal hemodynamics. Increased NaCl in the thick ascending limb stimulate O_2^- generation. However, we do not know whether physiological changes in NaCl concentration augment O_2^- generation, nor the mediator(s) involved. In other cells Rac1, a regulatory subunit of NADPH oxidase, is activated by elevated NaCl. We hypothesized that increasing luminal NaCl within the physiological range activates Rac1 and NADPH oxidase and thereby increases O_2^- production. We increased NaCl from 10 to 57 mM in medullary thick ascending limb suspensions and measured O_2^- generation using lucigenin and Rac1 activity using Western blot. Increasing NaCl stimulated O_2^- generation from 1.40 \pm 0.17 to 2.71 \pm 0.30 nmol O_2^- /min/mg protein ($n=6$; $p<0.05$). This increase was blocked by the Na/K/2Cl cotransporter inhibitor furosemide and the NADPH oxidase inhibitor apocynin. To examine the role of Rac1 in NaCl-induced O_2^- production, we measured Rac1 translocation by Western blot. When we added NaCl, Rac1 in the particulate fraction increased from 6.8 \pm 0.8 to 11.7 \pm 2.4% of total Rac1 ($n=7$; $p<0.05$). Then we measured O_2^- generation in the presence and absence of the Rac1 inhibitor. In the absence of the Rac1 inhibitor, NaCl increased O_2^- generation from 1.07 \pm 0.24 to 2.02 \pm 0.49 nmol O_2^- /min/mg protein, and this increase was completely blocked by the inhibitor. Similarly, in vivo treatment of thick ascending limbs with adenovirus expressing dominant-negative Rac1 decreased NaCl-induced O_2^- generation by 60% compared to control (0.33 \pm 0.04 vs. 0.81 \pm 0.17 nmol O_2^- /min/mg protein; $n=6$; $p<0.05$). We concluded that physiological increases in NaCl stimulate thick ascending limb O_2^- generation by activating Rac1. Key words: NKCC2, superoxide, reactive oxygen specie.

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Hypertension & Vascular Research

Silva, G. B. and J. L. Garvin (2009). "Extracellular ATP inhibits transport in medullary thick ascending limbs: role of P2X receptors." American Journal of Physiology-Renal Physiology **297**(5): F1168-F1173. [PDF Full-Text](#)

[Silva, Guillermo B.; Garvin, Jeffrey L.] Henry Ford Hosp, Div Hypertens & Vasc Res, Detroit, MI 48202 USA.
[Garvin, Jeffrey L.] Wayne State Univ, Sch Med, Dept Physiol, Detroit, MI 48201 USA.
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Silva GB, Garvin JL. Extracellular ATP inhibits transport in medullary thick ascending limbs: role of P2X receptors. *Am J Physiol Renal Physiol* 297: F1168-F1173, 2009. First published August 26, 2009; doi: 10.1152/ajprenal.00325.2009.-Absorption of NaCl by the thick ascending limb (TAL) involves active transport and therefore depends on oxidative phosphorylation. Extracellular ATP has pleiotropic effects, including both stimulation and inhibition of transport and inhibition of oxidative phosphorylation. However, it is unclear whether ATP alters TAL transport and how this occurs. We hypothesized that ATP inhibits TAL Na absorption by reducing Na entry. We measured oxygen consumption in TAL suspensions. ATP reduced oxygen consumption in a concentration-dependent manner. The purinergic (P2) receptor antagonist suramin (300 μ M) blocked the effect of ATP on TAL oxygen consumption (147 \pm 15 vs. 146 \pm 16 nmol O₂.min⁻¹.mg protein⁻¹). In contrast, the adenosine receptor antagonist theophylline did not block the effect of ATP on oxygen consumption. When Na-K-2Cl cotransport and Na/H exchange were blocked with furosemide (100 μ M) plus dimethyl amiloride (100 μ M), ATP did not inhibit TAL oxygen consumption (from 78 \pm 13 to 98 \pm 5 nmol O₂.min⁻¹.mg protein⁻¹). The Na ionophore nystatin (200 U/ml) increased TAL oxygen consumption to a similar extent in both ATP- and vehicle-treated samples (368 \pm 41 vs. 397 \pm 47 nmol O₂.min⁻¹.mg protein⁻¹). The nitric oxide synthase inhibitor N-G-nitro-L-arginine methyl ester (3 mM) blocked the ATP effects on TAL oxygen consumption (157 \pm 10 vs. 165 \pm 15 nmol O₂.min⁻¹.mg protein⁻¹). The P2X-selective receptor antagonist NF023 blocked the effect of ATP on oxygen consumption, whereas the P2X-selective agonist beta-gamma-Me-ATP reduced oxygen consumption in a concentration-dependent manner. We conclude that ATP inhibits Na transport-related oxygen consumption in TALs by reducing Na entry and P2X receptors and nitric oxide mediate this effect.

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Hypertension & Vascular Research

Yingst, D. R., A. Araghi, T. M. Doci, R. Mattingly and W. H. Beierwaltes (2009). "Decreased renal perfusion rapidly increases plasma membrane Na-K-ATPase in rat cortex by an angiotensin II-dependent mechanism." American Journal of Physiology-Renal Physiology **297**(5): F1324-F1329. [PDF Full-Text](#)

[Yingst, Douglas R.; Doci, Tabitha M.; Beierwaltes, William H.] Wayne State Univ, Sch Med, Dept Physiol, Detroit, MI 48201 USA. [Araghi, Ali] Wayne State Univ, Sch Med, Dept Internal Med, Div Pulm Allergy Crit Care & Sleep Med, Detroit, MI 48201 USA. [Mattingly, Raymond] Wayne State Univ, Sch Med, Dept Pharmacol, Detroit, MI 48201 USA. [Beierwaltes, William H.] Henry Ford Hosp, Div Hypertens & Vasc Res, Detroit, MI 48202 USA.
Yingst, DR, Wayne State Univ, Sch Med, Dept Physiol, 540 E Canfield Ave, Detroit, MI 48201 USA.
dyingst@med.wayne.edu

Yingst DR, Araghi A, Doci TM, Mattingly R, Beierwaltes WH. Decreased renal perfusion rapidly increases plasma membrane Na-K-ATPase in rat cortex by an angiotensin II-dependent mechanism. *Am J Physiol Renal Physiol* 297: F1324-F1329, 2009. First published September 2, 2009; doi: 10.1152/ajprenal.90363.2008.-To understand how rapid changes in blood pressure can regulate Na-K-ATPase in the kidney cortex, we tested the hypothesis that a short-term (5 min) decrease in renal perfusion pressure will increase the amount of Na-K-ATPase in the plasma membranes by an angiotensin II-dependent mechanism. The abdominal aorta of anesthetized Sprague-Dawley rats was constricted with a ligature between the renal arteries, and pressure was monitored on either side during acute constriction. Left renal perfusion pressure was reduced to 70 \pm 1 mmHg (n = 6), whereas right renal perfusion pressure was 112 \pm 4 mmHg. In control (nonconstricted) rats (n = 5), pressure to both kidneys was similar at 119 \pm 6 mmHg. After 5 min of reduced perfusion, femoral venous samples were taken for plasma renin activity (PRA) and the kidneys excised. The cortex was dissected, minced, sieved, and biotinylated. Lower perfusion left kidneys showed a 41% increase (P < 0.003)

in the amount of Na-K-ATPase in the plasma membrane compared with right kidneys. In controls, there was no difference in cell surface Na-K-ATPase between left and right kidneys ($P = 0.47$). PRA was 57% higher in experimental animals compared with controls. To test the role of angiotensin II in mediating the increase in Na-K-ATPase, we repeated the experiments ($n = 6$) in rats treated with ramiprilat. When angiotensin-converting enzyme was inhibited, the cell surface Na-K-ATPase of the two kidneys was equal ($P = 0.46$). These results confirm our hypothesis: rapid changes in blood pressure regulate trafficking of Na-K-ATPase in the kidney cortex.

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Infectious Diseases

Sun, H. Y., B. D. Alexander, O. Lortholary, F. Dromer, G. N. Forrest, G. M. Lyon, J. Somani, K. L. Gupta, R. del Busto, T. L. Pruett, C. D. Sifri, A. P. Limaye, G. T. John, G. B. Klintmalm, K. Pursell, V. Stosor, M. I. Morris, L. A. Dowdy, P. Munoz, A. C. Kalil, J. Garcia-Diaz, S. Orloff, A. A. House, S. Houston, D. Wray, S. Huprikar, L. B. Johnson, A. Humar, R. R. Razonable, S. Husain and N. Singh (2009). "Lipid Formulations of Amphotericin B Significantly Improve Outcome in Solid Organ Transplant Recipients with Central Nervous System Cryptococcosis." *Clinical Infectious Diseases* **49**(11): 1721-1728. [PDF Full-Text](#)

[Husain, Shahid; Singh, Nina] Univ Pittsburgh, Pittsburgh, PA USA. [Sun, Hsin-Yun; Singh, Nina] VA Pittsburgh Healthcare Syst, Pittsburgh, PA USA. [Alexander, Barbara D.] Duke Univ, Med Ctr, Durham, NC USA. [Forrest, Graeme N.] Univ Maryland, Sch Med, Baltimore, MD 21201 USA. [Lyon, G. Marshall; Somani, Jyoti] Emory Univ, Atlanta, GA 30322 USA. [del Busto, Ramon] Henry Ford Hosp, Detroit, MI 48202 USA. [Johnson, Leonard B.] St Johns Hosp, Detroit, MI USA. [Pruett, Timothy L.; Sifri, Costi D.] Univ Virginia, Charlottesville, VA USA. [Limaye, Ajit P.] Univ Washington, Seattle, WA 98195 USA. [Klintmalm, Goran B.] Baylor Univ, Med Ctr, Dallas, TX USA. [Pursell, Kenneth] Univ Chicago, Chicago, IL 60637 USA. [Stosor, Valentina] Northwestern Univ, Chicago, IL 60611 USA. [Morris, Michelle I.; Dowdy, Lorraine A.] Univ Miami, Miller Sch Med, Miami, FL 33136 USA. [Houston, Sally] Tampa Gen Hosp, Tampa, FL 33606 USA. [Kalil, Andre C.] Univ Nebraska, Omaha, NE 68182 USA. [Garcia-Diaz, Julia] Alton Ochsner Med Fdn & Ochsner Clin, New Orleans, LA 70121 USA. [Orloff, Susan] Oregon Hlth & Sci Univ, Portland, OR USA. [Wray, Dannah] Med Univ S Carolina, Charleston, SC 29425 USA. [Huprikar, Shirish] Mt Sinai Med Ctr, New York, NY 10029 USA. [Razonable, Raymund R.] Mayo Clin, Rochester, MN USA. [Sun, Hsin-Yun] Natl Taiwan Univ, Coll Med, Taipei 10764, Taiwan. [Sun, Hsin-Yun] Natl Taiwan Univ Hosp, Dept Internal Med, Taipei 100, Taiwan. [Dromer, Françoise] Inst Pasteur, Paris, France. [Lortholary, Olivier] Hop Necker Enfants Malad, Fac Med Paris Descartes, Paris, France. [Lortholary, Olivier] Hop Necker Enfants Malad, Inst Pasteur, Paris, France. [Gupta, Krishan L.] Postgrad Inst Med Educ & Res, Chandigarh 160012, India. [John, George T.] Christian Med Coll & Hosp, Vellore, Tamil Nadu, India. [Munoz, Patricia] Hosp Gen Univ Gregorio Maranon, Madrid, Spain. [Munoz, Patricia] CIBER Enfermedades Resp, Madrid, Spain. [House, Andrew A.] Univ Western Ontario, London, ON, Canada. [Humar, Atul] Toronto Gen Hosp, Univ Hlth Network, Toronto, ON, Canada. Singh, N, VA Med Ctr, Infect Dis Sect, Univ Dr C, Pittsburgh, PA 15240 USA. nis5@pitt.edu

Background. Whether outcome of central nervous system (CNS) cryptococcosis in solid organ transplant recipients treated with lipid formulations of amphotericin B is different from the outcome of the condition treated with amphotericin B deoxycholate (AmBd) is not known. **Methods.** We performed a multicenter study involving a cohort comprising consecutive solid organ transplant recipients with CNS cryptococcosis. **Results.** Of 75 patients treated with polyenes as induction regimens, 55 (73.3%) received lipid formulations of amphotericin B and 20 (26.7%) received AmBd. Similar proportions of patients in both groups had renal failure at baseline ($P = .94$). Overall, mortality at 90 days was 10.9% in the group that received lipid formulations of amphotericin B and 40.0% in the group that received AmBd. In univariate analysis, nonreceipt of calcineurin inhibitors ($P = .034$), renal failure at baseline ($P = .016$), and fungemia ($P = .003$) were significantly associated with mortality. Compared with AmBd, lipid formulations of amphotericin B were associated with a lower mortality ($P = .007$). Mortality did not differ between patients receiving lipid formulations of amphotericin B with or without flucytosine ($P = .349$). In stepwise logistic regression analysis, renal failure at baseline (odds ratio [OR], 4.61; 95% confidence interval [CI], 1.02-20.80; $P = .047$) and fungemia (OR, 10.66; 95% CI, 2.08-54.55; $P = .004$) were associated with an increased mortality, whereas lipid formulations of amphotericin B were associated with a lower mortality (OR, 0.11; 95% CI, 0.02-0.57; $P = .008$). **Conclusions.** Lipid formulations of amphotericin B were independently associated with better outcome and may be considered as the first-line treatment for CNS cryptococcosis in these patients.

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Internal Medicine

Kaatz, S. (2009). "What you should know about the 2008 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th) on Antithrombotic and Thrombolytic Therapy." J Thromb Thrombolysis **Epub Ahead of Print**. [PDF Full-Text](#)

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The American College of Chest Physicians published their first consensus conference guidelines on antithrombotic therapy in 1986 and has updated these guidelines approximately every 3 years as a supplement to the journal Chest. These guidelines are widely accepted as an authoritative source of information and considered by many to be the textbook for antithrombotic therapy. The most recent guidelines are from the 8th consensus conference, published in 2008, and this article will highlight new recommendations that have evolved since the 2004 Chest supplement. Examples from the literature that support the evolution these guidelines will focus on changes that are most germane to the majority of attendees at the 10th National Conference on Anticoagulant Therapy and members of the AC Forum. The objective of this article is to help answer ten common clinical questions frequently faced by anticoagulation management services.

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Internal Medicine

Kaatz, S. (2009). "Impact on patient care: patient case through the continuum of care." J Thromb Thrombolysis **Epub Ahead of Print**. [PDF Full-Text](#)

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Hospitalized patients are at increased risk of venous thromboembolism and the Joint Commission has initiated practice measures to improve the rates of preventable events. The Joint Commission also initiated the National Patient Safety Goals for medication prescribing and administration, of which, goal 03.05.01 is specifically aimed at anticoagulation therapy. These measures and goals are consistent with the American College of Chest Physicians' Consensus Guidelines on Antithrombotic and Thrombolytic Therapy. This narrative review uses a case-based approach that brings up practical clinical questions regarding these measures, goals and guidelines as they apply to a patient going through the continuum of care from the hospital to their home.

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Nephrology

Thalla, R., D. Kim, K. K. Venkat and R. Parasuraman (2009). "Sequestration of active *Cryptococcus neoformans* infection in the parathyroid gland despite prolonged therapy in a renal transplant recipient." Transpl Infect Dis **11(4)**: 349-52. [PDF Full-Text](#)

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Disseminated cryptococcal infection occurs mainly in the immunocompromised host, particularly in those with impaired cellular immunity. The treatment outcome depends not only on the duration and choice of antifungal therapy, but also on the activity of the organism to persist in different parts of the body despite therapy. We present a case of persistence of cryptococcal infection in the parathyroid gland in a kidney transplant recipient. A 38-year-old male renal transplant recipient diagnosed to have disseminated cryptococcosis was treated with discontinuation of immunosuppression, amphotericin B, and flucytosine for 2 weeks, and fluconazole subsequently. Dialysis was initiated when graft function deteriorated after discontinuation of immunosuppression. The patient showed no clinical signs of active cryptococcal infection on fluconazole therapy. One year after the diagnosis of cryptococcosis, and still on fluconazole, he underwent parathyroidectomy, for severe secondary hyperparathyroidism. Surprisingly, active cryptococcal infection with necrotizing granulomatous inflammation was demonstrated in the parathyroid, despite being on therapy. This patient illustrates that persistence of fungal infection despite prolonged therapy can occur in unusual sites such as the parathyroid and may be a source for future recurrence and dissemination.

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Neurology

Cerghet, M., L. Schultz and S. Elias (2009). "Serum 25-hydroxyvitamin D level is lower in black patients with multiple sclerosis." Multiple Sclerosis **15**(11): 1400-1400. [Article Request Form](#)

[Cerghet, Mirela; Schultz, Lonni; Elias, Stanton] Henry Ford Hlth Syst, Dept Neurol, Detroit, MI USA. [Schultz, Lonni] Henry Ford Hlth Syst, Dept Epidemiol, Detroit, MI USA.

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Neurology

Cerghet, M., R. P. Skoff, M. Swamydas and D. Bessert (2009). "Sexual dimorphism in the white matter of rodents." Journal of the Neurological Sciences **286**(1-2): 76-80. [PDF Full-Text](#)

[Skoff, Robert P.; Bessert, Denise] Wayne State Univ, Sch Med, Detroit, MI 48202 USA. [Swamydas, Muthulekha] Univ N Carolina Charlotte, Charlotte, NC USA.

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Sexual dimorphism of astrocytes and neurons is well documented in many brain and spinal cord structures. Sexual dimorphism of oligodendrocytes (Olg) and myelin has received less attention. We recently showed that density of Olg in corpus callosum, fornix, and spinal cord of wild-type male rodents is more densely packed than in females; myelin proteins and myelin gene expression are likewise greater in males than in female rodents. However, glial cell proliferation and cell death were two times greater in female corpus callosum. Endogenous sex hormones, specifically lack of androgens, produce an Olg female phenotype in castrated male mouse. In vitro studies Using OlgS Culture also showed differences between males and females Olg survival and signaling pathways in response to sexual hormones. Sexual dimorphism of white matter tracts and glia in rodents indicates the necessity for controlling gender in the experimental studies of neurodegenerative disorders. Most importantly, our studies suggest that hormones may contribute to sexual dimorphism observed in certain human diseases including multiple sclerosis. (C) 2009 Elsevier B.V. All rights reserved.

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Neurology

Chen, J., X. Cui, A. Zacharek and M. Chopp (2009). "Increasing Ang1/Tie2 expression by simvastatin treatment induces vascular stabilization and neuroblast migration after stroke." J Cell Mol Med **13**(7): 1348-57. [Article Request Form](#)

Department of Neurology, Henry Ford Hospital, Detroit, MI 48202, USA. jieli@neuro.hfh.edu

In this study, we tested the hypothesis that the Angiopoietin 1 (Ang1)/Tie2 pathway mediates simvastatin-induced vascular integrity and migration of neuroblasts after stroke. Rats were subjected to 2 hrs of middle cerebral artery occlusion (MCAo) and treated, starting 1 day after stroke with or without simvastatin (1 mg/kg, daily) for 7 days. Simvastatin treatment significantly decreased blood-brain barrier (BBB) leakage and concomitantly, increased Ang1, Tie2 and Occludin expression in the ischaemic border (IBZ) compared to the MCAo control group. Simvastatin also significantly increased doublecortin (DCX, a marker of migrating neuroblasts) expression in the IBZ compared to control MCAo rats. DCX was highly expressed around vessels. To further investigate the signalling pathway of simvastatin-induced vascular stabilization and angiogenesis, rat brain microvascular endothelial cell (RBMEC) culture was employed. The data show that simvastatin treatment of RBMEC increased Ang1 and Tie2 gene and protein expression and promoted phosphorylated-Tie2 activity. Simvastatin significantly increased endothelial capillary tube formation, an index of angiogenesis, compared to non-treated control. Inhibition of Ang1 or knockdown of Tie2 gene expression in endothelial cells significantly attenuated simvastatin-induced capillary tube formation. In addition, simvastatin significantly increased subventricular zone (SVZ) explant cell migration compared to non-treatment control. Inhibition of Ang1 significantly attenuated simvastatin-induced SVZ cell migration. Simvastatin treatment of stroke increases Ang1/Tie2 expression and thereby reduces BBB leakage and promotes vascular stabilization. Ang1/Tie2 expression induced by simvastatin treatment promotes neuroblast micro-vascular coupling after stroke.

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Neurology

Chopp, M., G. K. Steinberg, D. Kondziolka, M. Lu, T. M. Bliss, Y. Li, D. C. Hess and C. V. Borlongan (2009). "Who's in Favor of Translational Cell Therapy for Stroke: STEPS Forward Please?" Cell Transplantation **18**(7): 691-693. [Article Request Form](#)

[Borlongan, Cesario V.] Univ S Florida, Dept Neurosurg, Tampa, FL 33612 USA. [Chopp, Michael; Lu, Mei; Li, Yi] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA. [Steinberg, Gary K.; Bliss, Tonya M.] Stanford Univ, Dept Neurosurg, Sch Med, Stanford, CA 94305 USA. [Kondziolka, Douglas] Univ Pittsburgh, Dept Neurol Surg, Pittsburgh, PA 15260 USA. [Hess, David C.; Borlongan, Cesario V.] Med Coll Georgia, Dept Neurol, Augusta, GA 30912 USA.
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A consortium of translational stem cell and stroke experts from multiple academic institutes and biotechnology companies, under the guidance of the government (FDA/NIH), is missing. Here, we build a case for the establishment of this consortium if cell therapy for stroke is to advance front the laboratory to the clinic

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Neurology

Hacein-Bey, L. and P. N. Varelas (2009). "Pedunculated Basilar Terminus Aneurysm with Pseudo-Septation due to Anterior Herniation through a Perforated Membrane of Lilliequist." American Journal of Neuroradiology **30**(9): 1688-1690. [PDF Full-Text](#)

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Septations within cerebral arteries or aneurysms are exceedingly rare in the absence of associated fenestrations. We report an unusual unruptured pedunculated basilar apex aneurysm, with a "pseudoseptation" between the main aneurysmal sac and an anterior compartment, which was, in fact, represented by a perforation in the membrane of Lilliequist, permitting anterior aneurysmal herniation into the carotid-chiasmatic cistern. The patient was successfully treated with detachable coils. This case is unusual on 2 accounts: 1) the aneurysm's appearance, and 2) the presence of a large fenestration in the membrane of Lilliequist, of which anatomic features are herein reviewed.

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Neurology

Heliopoulos, J., K. Vadikolias, C. Piperidou and P. Mitsias (2009). "Detection of Carotid Artery Plaque Ulceration Using 3-Dimensional Ultrasound." J Neuroimaging **Epub Ahead of Print**. [Article Request Form](#)

From the Department of Neurology, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece (JH, KV, CP); Stroke and Neurovascular Center, Department of Neurology, Henry Ford Health System, Detroit, Michigan (PM).

ABSTRACT BACKGROUND Three-dimensional (3D) ultrasound imaging is a new technique that maximizes the information and image quality of traditional 2-dimensional (2D) B-mode scanning. The aim of this study was to evaluate the ability of the 3D ultrasound technique to characterize ulcerated atherosclerotic carotid plaque. **METHODS** Using conventional 2D ultrasound, we examined 284 carotid arteries from 142 consecutive patients (101 men and 41 women; average age, 64 years). Eighty-two carotid arteries were symptomatic with atherosclerotic plaque causing 50-99% stenosis. In 62 arteries, the atherosclerotic plaques were visualized completely and were further processed to construct 3D images. Two independent observers rated plaque morphology according to a standardized protocol. **RESULTS** The 3D ultrasound showed carotid plaque ulceration more frequently than the 2D method (16.1% and 14.5% of plaques, for observers 1 and 2, respectively, versus 6.5% and 9.7% of plaques, for observers 1 and 2, respectively, $P = .125$ and $P = .063$, for

observers 1 and 2, respectively). The interobserver reproducibility was very good for both methods ($\kappa = .973$, $SE = .027$, $P < .001$ for 3D, and $\kappa = .885$, $SE = .055$, $P < .001$ for 2D), although the 3D method was slightly superior to 2D. CONCLUSIONS 3D ultrasound reliably characterized the surface morphology of atherosclerotic carotid plaques. A trend of superiority of 3D ultrasound over 2D was found in detecting ulcers of carotid artery plaque. *J Neuroimaging* 2009;XX:1-6.

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Neurology

Hu, J. N., W. Z. Feng, J. Hua, Q. Jiang, Y. Xuan, T. Li and E. M. Haacke (2009). "A high spatial resolution in vivo ¹H magnetic resonance spectroscopic imaging technique for the human breast at 3 T." *Medical Physics* **36**(11): 4870-4877. [Article Request Form](#)

[Hua, Jiani; Xuan, Yang; Li, Tao; Haacke, E. Mark] Wayne State Univ, Dept Radiol, Detroit, MI 48201 USA. [Feng, Wenzheng] Columbia Univ, Med Ctr, Dept Radiat Oncol, New York Presbyterian Hosp, New York, NY 10032 USA. [Hua, Jia] Shanghai Jiao Tong Univ, Sch Med, Shanghai 200127, Peoples R China. [Hua, Jia] Renji Hosp, Dept Radiol, Shanghai 200127, Peoples R China. [Jiang, Quan] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA. [Hua, Jiani] Harper Grace Hosp, MRC Concourse, Detroit, MI 48201 USA. Hu, JN, Wayne State Univ, Dept Radiol, Detroit, MI 48201 USA. jhu@med.wayne.edu

Purpose: The technical challenges that have prevented routine proton magnetic resonance spectroscopic imaging (¹H MRSI) examinations of the breast include insufficient spatial resolution, increased difficulties in shimming compared to the brain, and strong lipid contamination at short echo time (TE) at 1.5 T. The authors investigated the feasibility of high spatial resolution ¹H MRSI of human breast cancer in a clinical setting at 3 T. Methods: Ten patient studies (eight cancers and two benign lesions) were performed in a 3 T whole-body clinical imager using a pulse sequence consisting of optional outer volume presaturation, optional CHESS pulse for lipid suppression, CHESS pulse for water suppression, and standard 2D/3D PRESS pulse sequence with an elliptical weighted k-space sampling scheme. Results: All ten studies were technically successful. The spectral quality was acceptable for all cases even the one with a 65 Hz width of water peak at half height. Choline (Cho) signals were clearly visible in malignant lesion areas, while there was no detectable Cho in normal appearing breast or in benign lesions. It was also observed that the distribution of Cho signal can be nonuniform across MRI demonstrated lesions. Conclusions: To the author's knowledge, this is the first 2D/3D MRSI study of human breast cancer with short TE (less than 135 ms) at 3 T and the highest spatial resolution (up to 0.25 cm³) to date. In conclusion, the authors have presented a robust technique for high spatial resolution in vivo ¹H MRSI of human breast cancer that uses the combined advantages of high field, short TE, multivoxel, and high spatial resolution itself to overcome the major technical challenges and illustrated its potential for routine clinical examination as well as advantages over single-voxel techniques in studying metabolite heterogeneity. (C) 2009 American Association of Physicists in Medicine. [DOI: 10.1118/1.3213087]

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Neurology

Jiang, H., X. Shang, H. Wu, S. C. Gautam, S. Al-Holou, C. Li, J. Kuo, L. Zhang and M. Chopp (2009). "Resveratrol downregulates PI3K/Akt/mTOR signaling pathways in human U251 glioma cells." *J Exp Ther Oncol* **8**(1): 25-33. [Article Request Form](#)

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Resveratrol (trans-3,4', 5-trihydroxystilbene) is a naturally occurring polyphenolic compound that has antiinflammatory, antioxidant, neuroprotective properties and acts as a chemopreventive agent. Resveratrol causes cell cycle arrest and induces apoptotic cell death in various types of cancer cells. In the current studies, the effect of resveratrol on phosphoinositide kinase-3 (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway was examined in human U251 glioma cells. Resveratrol decreased both the expression and phosphorylation of Akt. Inhibitors of PI3K (LY294002) and Akt (SH-6) enhanced resveratrol-induced LDH release and caspase-3 activation. Resveratrol reduced phosphorylation of ribosomal protein S6 and the mTOR inhibitor rapamycin further enhanced resveratrol-induced cell death. These results suggest that the downregulation of PI3K/Akt/mTOR signaling pathways may be an important mediator in resveratrol-induced apoptosis in glioma cells.

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Neurology

Li, L., Q. Jiang, G. Ding, L. Zhang, Z. G. Zhang, Q. Li, S. Panda, M. Lu, J. R. Ewing and M. Chopp (2009). "Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study." J Cereb Blood Flow Metab **EPub Ahead of Print**. [Article Request Form](#)

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

We tested the hypotheses that administration routes affect the migration and distribution of grafted neural progenitor cells (NPCs) in the ischemic brain and that the ischemic lesion plays a role in mediating the grafting process. Male Wistar rats (n=41) were subjected to 2-h middle cerebral artery occlusion (MCAo), followed 1 day later by administration of magnetically labeled NPCs. Rats with MCAo were assigned to one of three treatment groups targeted for cell transplantation intra-arterially (IA), intracisternally (IC), or intravenously (IV). MRI measurements consisting of T2-weighted imaging and three-dimensional (3D) gradient echo imaging were performed 24 h after MCAo, 4 h after cell injection, and once a day for 4 days. Prussian blue staining was used to identify the labeled cells, 3D MRI to detect cell migration and distribution, and T2 map to assess lesion volumes. Intra-arterial (IA) administration showed significantly increased migration, a far more diffuse distribution pattern, and a larger number of transplanted NPCs in the target brain than IC or IV administration. However, high mortality with IA delivery (IA: 41%; IC: 17%; IV: 8%) poses a serious concern for using this route of administration. Animals with smaller lesions at the time of transplantation have fewer grafted cells in the parenchyma. *Journal of Cerebral Blood Flow & Metabolism* advance online publication, 4 November 2009; doi:10.1038/jcbfm.2009.238.

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Neurology

Zachry, W. M., Q. D. Doan, B. J. Smith, J. D. Clewell and J. M. Griffith (2009). "Direct medical costs for patients seeking emergency care for losses of epilepsy control in a US managed care setting." Epilepsy & Behavior **16(2)**: 268-273. [PDF Full-Text](#)

[Zachry, Woodie M., III; Doan, Quynhchau D.; Clewell, Jerry D.; Griffith, Jenny M.] Abbott Labs, Abbott Pk, IL 60064 USA. [Smith, Brien J.] Henry Ford Hosp, Detroit, MI 48202 USA. Zachry, WM, Abbott Labs, 200 Abbott Pk Rd, Abbott Pk, IL 60064 USA. woodie.zachry@abbott.com

The objective of this retrospective claims database study was to compare the costs of care from a U.S. payer perspective before and after epilepsy treatment in emergent care settings and, secondarily, to describe the frequency of toxic effects and physical injuries occurring on the date of the emergent care. Nine and four-tenths percent of patients receiving emergent care for epilepsy (11411213) had an injury or adverse antiepileptic drug effect on the same date. The majority of incidents were superficial injuries and contusions (28%), fractures (21%), open wounds or injury to blood vessels (19%), intracranial injury (10%), and/or medication toxicity (10%). Both non-epilepsy-related (US\$12,745.56) and epilepsy-related (US\$2013.62) direct medical costs of care pre-index were significantly different from those post-index (US\$15,274.95 and US\$7087.53, respectively). The cost of care for possible reestablishment of epilepsy control and treatment of co-occurring injuries is significant when compared with that for the period prior to seizure. (C) 2009 Elsevier Inc. All rights reserved.

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Neurology

Zhang, L., M. Chopp, L. F. Jia, Y. S. Cui, M. Lu and Z. G. Zhang (2009). "Atorvastatin extends the therapeutic window for tPA to 6 h after the onset of embolic stroke in rats." Journal of Cerebral Blood Flow and Metabolism **29(11)**: 1816-1824. [Article Request Form](#)

[Zhang, Li; Chopp, Michael; Jia, Longfei; Cui, Yisheng; Zhang, Zheng Gang] Henry Ford Hlth Syst, Dept Neurol, Detroit, MI 48202 USA. [Chopp, Michael] Oakland Univ, Dept Phys, Rochester, MI USA. [Lu, Mei] Henry Ford Hlth Syst, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA. Zhang, ZG, Henry Ford Hlth Syst, Dept Neurol, 2799 W Grand Blvd, Detroit, MI 48202 USA. zhazh@neuro.hfh.edu

We investigated the neuroprotective effect of atorvastatin in combination with delayed thrombolytic therapy in a rat model of embolic stroke. Rats subjected to embolic middle cerebral artery (MCA) occlusion were treated

with atorvastatin at 4 h, followed by tissue plasminogen activator (tPA) at 6 or 8 h after stroke. The combination of atorvastatin at 4 h and tPA at 6 h significantly decreased the size of the embolus at the origin of the MCA, improved microvascular patency, and reduced infarct volume, but did not increase the incidence of hemorrhagic transformation compared with vehicle-treated control animals. However, monotherapy with tPA at 6 h increased the incidence of hemorrhagic transformation and failed to reduce infarct volume compared with the control group. In addition, adjuvant treatment with atorvastatin at 4 h and with tPA at 6 h reduced tPA-induced upregulation of protease-activated receptor-1, intercellular adhesion molecule-1, and matrix metalloproteinase-9, and concomitantly reduced cerebral microvascular platelet, neutrophil, and fibrin deposition compared with rats treated with tPA alone at 6 h. In conclusion, a combination of atorvastatin and tPA extended the therapeutic window for stroke to 6 h without increasing the incidence of hemorrhagic transformation. Atorvastatin blocked delayed tPA-potentiated adverse cerebral vascular events, which likely contributes to the neuroprotective effect of the combination therapy. *Journal of Cerebral Blood Flow & Metabolism* (2009) 29, 1816-1824; doi:10.1038/jcbfm.2009.105; published online 29 July 2009

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Neurology

Zheng, X., F. Jiang, M. Katakowski, Z. G. Zhang, Q. E. Lu and M. Chopp (2009). "ADAM17 promotes breast cancer cell malignant phenotype through EGFR-PI3K-AKT activation." *Cancer Biol Ther* 8(11): 1045-54. PMC2766867. [Article Request Form](#)

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

A disintegrin and metalloproteinase-17 (ADAM17) is involved in proteolytic ectodomain shedding of several membrane-bound growth factors and cytokines. The expression and activity of ADAM17 increase under some pathological conditions such as stroke and glioma. ADAM17 promotes neural progenitor cell migration and contributes to stroke-induced neurogenesis after stroke and brain tumor growth and invasion. In the present study, we sought to elucidate whether ADAM17 contributes to breast cancer progression and its mechanisms. To this end, we examined the role of ADAM17 in the proliferation, invasion and tube formation of MDA-MB-231 breast cancer cells in vitro. Stable transfection of the MDA-MB-231 cell line with either a plasmid for overexpression of human ADAM17, or a siRNA to ADAM17 was employed in this study to establish high or low ADAM17 expression in breast cancer cells, respectively. For study of mechanism, the ADAM17 inhibitor TAPI-2 and the PI3K-AKT inhibitor LY294002 were used to counteract high ADAM17 expression or the activated PI3K-AKT pathway. Proliferation of MDA-MB-231 breast cancer cells were tested by MTT, Bromodeoxyuridine incorporation assay, growth curve and sulforhodamine B assay. Matrigel invasion assays were used to assess the ability of MDA-MB-231 cells to penetrate the Extra Cellular Matrix. A Matrigel tube formation assay was performed to test capillary tube formation ability. EGFR-PI3K-Akt pathway activation in MDA-MB-231 cells under different ADAM17 expression levels were tested by western blot and ELISA. Our data show that ADAM17 promotes the MDA-MB-231 malignant phenotype by increased proliferation, invasion and angiogenesis. TGF α , VEGF secretion and VEGF expression was increasing by ADAM17 and counteracted by ADAM17 siRNA, TAPI-2 and LY294002 in MDA-MB-231 cells. ADAM17 activated, whereas ADAM17 siRNA, TAPI-2 and LY294002 deactivated the EGFR-PI3K-AKT signal pathway, which correlated with MDA-MB-231 cell malignant phenotype changes. This study suggests ADAM17 contributes to breast cancer progression through activation of the EGFR-PI3K-AKT signal pathway.

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Neurosurgery

Decarvalho, A. C., K. Nelson, N. Lemke, N. L. Lehman, A. S. Arbab, S. Kalkanis and T. Mikkelsen (2009). "Gliosarcoma Stem Cells Undergo Glial and Mesenchymal Differentiation In Vivo." *Stem Cells*. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Hospital, Detroit, MI 48202.

Cancer stem cells (CSCs) are characterized by their self-renewing potential, and by their ability to differentiate and phenocopy the original tumor in orthotopic xenografts. Long term propagation of glioblastoma (GBM) cells in serum containing medium results in loss of the CSCs and outgrowth of cells genetically and biologically divergent from the parental tumors. In contrast, the use of neurosphere assay, a serum-free culture for selection and propagation of CNS-derived stem cells, allows the selection of a subpopulation containing CSCs. Gliosarcoma (GS), a morphological variant comprising approximately 2% of GBMs, present a biphasic growth pattern, composed of glial and metaplastic mesenchymal components. To assess whether the neurosphere

assay would allow the amplification of a subpopulation of cells with "gliosarcoma stem cell" properties, capable of propagating both components of this malignancy, we have generated neurospheres and serum cultures from primary GS and GBM surgical specimens. Neurosphere cultures from GBM and GS samples expressed neural stem cell markers Sox2, Msi1 and Nestin. In contrast to the GBM neurosphere lines, the GS neurospheres were negative for the stem cell marker CD133. All neurosphere lines generated high grade invasive orthotopic tumor xenografts, with histological features strikingly similar to the parental tumors, demonstrating that these cultures indeed are enriched in CSCs. Remarkably, low passage GS serum cultures retained the expression of stem cell markers, the ability to form neurospheres, and tumorigenicity. The GS experimental tumors phenocopied the parental tumor, exhibiting biphasic glial and mesenchymal components, constituting a clinically relevant model to investigate mesenchymal differentiation in GBMs.

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Neurosurgery

Wu, H., H. Jiang, D. Lu, Y. Xiong, C. Qu, D. Zhou, A. Mahmood and M. Chopp (2009). "Effect of simvastatin on glioma cell proliferation, migration, and apoptosis." Neurosurgery **65**(6): 1087-96; discussion 1096-7. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan 48202, USA.

OBJECTIVE: In this study, we investigated the effects of simvastatin on proliferation, migration, and apoptosis in human U251 and U87 glioma cells and the underlying molecular mechanism. **METHODS:** We used colony formation assay to test the cell proliferation, in vitro scratch assay to examine the cell migration, and caspase-3 activity assay, annexin V staining, and cytochrome C release to evaluate the cell apoptosis. Lipid raft fractions were isolated from glioma cells. Total cholesterol content assay was used to test the change of cholesterol level in lipid raft fractions. Immunocytochemistry staining was performed to detect the changes of lipid rafts in cell membranes. Western blotting analysis was performed to examine the signal transduction both in cells and in lipid raft fractions. **RESULTS:** Simvastatin inhibited proliferation and migration of U251 and U87 cells dose dependently. Simvastatin induced an increase of caspase-3 activity and annexin V staining, and down-regulated the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. Simvastatin also decreased cholesterol content in lipid raft fractions, suppressed caveolin-1 expression in the lipid rafts, and induced Fas translocation into lipid rafts, suggesting that simvastatin may inhibit the prosurvival PI3K/Akt pathway and trigger caspase-3-dependent apoptotic cell death through the modulation of lipid rafts. **CONCLUSION:** These results suggest that modulation of lipid rafts, Fas translocation, and PI3K/Akt/caspase-3 pathway are involved in the antitumor effect of simvastatin and may have a potential role in cancer prevention and treatment.

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Obstetrics & Gynecology

George, A., D. Eisenstein and G. Wegienka (2009). "Analysis of the impact of body mass index on the surgical outcomes after robot-assisted laparoscopic myomectomy." J Minim Invasive Gynecol **16**(6): 730-3. [PDF Full-Text](#)

Departments of Obstetrics and Gynecology, Henry Ford Hospital, Detroit, Michigan.

STUDY OBJECTIVE: To estimate the impact of body mass index (BMI) on surgical outcomes in patients undergoing robotic myomectomy. **DESIGN:** A retrospective cohort data analysis (Canadian Task Force classification II-2). **SETTING:** Community-based teaching hospital. **PATIENTS:** A total of 77 consecutive patients from January 2005 through November 2008 with symptomatic leiomyomata. **INTERVENTION:** Robotic-assisted laparoscopic myomectomy. **MEASUREMENTS AND MAIN RESULTS:** Body mass index ([BMI] expressed as kg/m²) was abstracted from the medical charts of all patients undergoing robotic myomectomy. Data on estimated blood loss, procedure time, length of hospital stay, diameter of the largest fibroid, and specimen weight were also extracted. Overall patient demographics between the groups were similar. Thirty-two patients (41.6%) were obese or morbidly obese (BMI>30). The parameters analyzed for associations with the continuous measure of BMI included length of postoperative hospital stay (LOS), estimated blood loss (EBL), and procedure duration. Median (range) procedure time among all patients was (195 minutes, 98-653 minutes), estimated blood loss was (100 mL, 10-700 mL), and length of hospital stay was (1 day, 1-5 days). No associations were determined between BMI and LOS (r=0.14, p=.22), EBL (r=0.25, p=.03), or procedure duration (r=0.16, p=.22) with Spearman correlations. The size of the largest leiomyoma diameter did not affect these associations. **CONCLUSION:** Preoperative obesity is not a risk factor for poor surgical outcome in patients undergoing robotic myomectomy.

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Obstetrics & Gynecology

Sanses, T. V. D., A. Shahryarnejad, S. Molden, K. A. Hoskey, S. Abbasy, D. Patterson, E. K. Saks, E. E. W. LeBrun, T. L. Gamble, V. G. King, A. L. Nguyen, H. Abed and S. B. Young (2009). "Anatomic outcomes of vaginal mesh procedure (Prolift) compared with uterosacral ligament suspension and abdominal sacrocolpopexy for pelvic organ prolapse: a Fellows' Pelvic Research Network study." [American Journal of Obstetrics and Gynecology](#) **201**(5).

[PDF Full-Text](#)

[Sanses, Tatiana V. D.; Hoskey, Kay A.] Univ Maryland, Med Ctr, Dept Obstet & Gynecol, Div Urogynecol & Reconstruct Pelv Surg, Baltimore, MD 21201 USA. [Sanses, Tatiana V. D.; Hoskey, Kay A.] Greater Baltimore Med Ctr, Dept Gynecol Female Urol & Pelv Surg, Baltimore, MD USA. [Shahryarnejad, Azin] Mt Sinai Sch Med, Dept Obstet & Gynecol, Div Female Pelv Med & Reconstruct Surg, New York, NY USA. St Lukes Hosp & Hlth Network, Dept Obstet & Gynecol, Div Urogynecol, Allentown, PA USA. [Molden, Stephanie] Inst Female Pelv Med & Reconstruct Surg, Allentown, PA USA. [Abbasy, Shameem] Loyola Univ, Med Ctr, Dept Obstet & Gynecol, Maywood, IL 60153 USA. [Patterson, Danielle] Brigham & Womens Hosp, Dept Obstet & Gynecol, Div Urogynecol, Boston, MA 02115 USA. [Saks, Emily K.] Univ Penn, Sch Med, Dept Obstet & Gynecol, Div Urogynecol, Philadelphia, PA 19104 USA. [LeBrun, Emily E. Weber; Young, Stephen B.] Univ Massachusetts, Mem Med Ctr, Div Urogynecol & Reconstruct Pelv Surg, Worcester, MA 01605 USA. [Gamble, Tondalaya L.; Nguyen, Aimee L.] Northwestern Univ, Evanston Continence Ctr, Evanston, IL USA. [Gamble, Tondalaya L.; Nguyen, Aimee L.] Northwestern Univ, Evanston Northshore Univ HealthSyst, Dept Obstet & Gynecol, Div Urogynecol, Evanston, IL USA. [King, Virginia G.] Oregon Hlth & Sci Univ, Dept Obstet & Gynecol, Div Urogynecol & Reconstruct Pelv Med, Portland, OR 97201 USA. [Abed, Husam] Henry Ford Hlth Syst, Dept Obstet & Gynecol, Div Female Pelv Med & Reconstruct Surg, Detroit, MI USA.

OBJECTIVE: The objective of the study was to compare apical support anatomic outcomes following vaginal mesh procedure (VMP) (Prolift) to uterosacral ligament suspension (USLS) and abdominal sacrocolpopexy (ASC). STUDY DESIGN: This multicenter, retrospective chart review compared apical anatomic success (stage 0 or 1 based on point C or D of the Pelvic Organ Prolapse Quantification), level of vaginal apex (point C or D) 3-6 months after prolapse repair at 10 US centers between 2004 and 2007. RESULTS: VMP, USLS, and ASC were performed for 206, 231, and 305 subjects respectively. There was no difference in apical success after VMP (98.8%) compared with USLS (99.1%) or ASC (99.3%) (both $P = 1.00$) 3-6 months after surgery. The average elevation of the vaginal apex was lower after VMP (-6.9 cm) than USLS (-8.05 cm) and ASC (-8.5 cm) (both $P < .001$) CONCLUSION: Patients undergoing VMP have similar apical success compared with USLS and ASC despite lower vaginal apex 3-6 month after surgery.

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Other

Dimenstein, I. B. (2009). "The Henry Ford Production System: reduction of surgical pathology in-process misidentification defects by bar code-specified work process standardization." [Am J Clin Pathol](#) **132**(6): 975-6; author reply 976-7. [PDF Full-Text](#)

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Pharmacy

Jennings, D. L. and M. L. Thompson (2009). "Use of Combination Therapy with a beta-Blocker and Milrinone in Patients with Advanced Heart Failure." [Annals of Pharmacotherapy](#) **43**(11): 1872-1876. [PDF Full-Text](#)

[Jennings, Douglas L.] Henry Ford Hosp, Dept Pharm, Detroit, MI 48201 USA. [Thompson, Melissa L.] Med Univ S Carolina, S Carolina Coll Pharm, Charleston, SC 29425 USA.

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OBJECTIVE: To review the literature evaluating the clinical effects of combination therapy with a beta-blocker and milrinone in patients with severe heart failure (HF). DATA SOURCES: Literature was accessed through MEDLINE (1950-June 2009), PubMed (1966-June 2009), and International Pharmaceutical Abstracts (1970-June 2009), with combinations-of the following terms: positive inotrope, milrinone, dobutamine, and beta-

receptor blocker. In addition, reference citations from publications identified were reviewed. **STUDY SELECTION AND DATA EXTRACTION:** All articles that examined the effect of combination therapy with a beta-blocker and milrinone on clinical endpoints in patients with advanced HF were assessed. **DATA SYNTHESIS:** A search of the literature revealed 4 studies examining the clinical effects of combination therapy with a beta-blocker and milrinone. Three of these studies were retrospective reviews, while one was a post hoc subgroup analysis from the OPTIME-CHF study. Concomitant therapy with milrinone and a P-blocker was well tolerated, with no significant increase in adverse events or deterioration in clinical status in any study. Tolerability rates for combination therapy ranged from 88% to 92%. In 2 of the studies, roughly 50% of the patients in the combination arm were able to be weaned off milrinone. One study suggested a mortality reduction in favor of combination therapy over milrinone therapy versus milrinone monotherapy. One study suggested a potential increase in mortality when P-blocker therapy was withdrawn in patients who were started on milrinone. None of the studies demonstrated any significant differences in hospitalization rates. All of the studies were limited by their retrospective nature and small sample size. **CONCLUSIONS:** Data are insufficient to make firm conclusions on the clinical benefit of combination therapy with a beta-blocker and milrinone in patients with advanced HF, although it appears that this regimen is well tolerated and may allow weaning of inotropic support.

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Radiation Oncology

Guan, H. Q., R. Hammoud and F. F. Yin (2009). "A positioning QA procedure for 2D/2D (kV/MV) and 3D/3D (CT/CBCT) image matching for radiotherapy patient setup." Journal of Applied Clinical Medical Physics **10**(4): 273-280. [Article Request Form](#)

[Guan, Huaqun] Good Samaritan Hlth Syst, Dept Radiat Oncol, Kearney, NE 68848 USA. [Hammoud, Rabih] Henry Ford River Ctr Oncol, Trenton, MI USA. [Yin, Fang-Fang] Duke Univ, Med Ctr, Dept Radiat Oncol, Durham, NC USA.

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huaiqunguan@catholichealth.net

A positioning QA procedure for Varian's 2D/2D (kV/MV) and 3D/3D (planCT/CBCT) matching was developed. The procedure was to check: (1) the coincidence of on-board imager (OBI), portal imager (PI), and cone beam CT (CBCT)'s isocenters (digital graticules) to a linac's isocenter (to a pre-specified accuracy); (2) that the positioning difference detected by 2D/2D (kV/MV) and 3D/3D(planCT/CBCT) matching can be reliably transferred to couch motion. A cube phantom with a 2 mm metal ball (bb) at the center was used. The bb was used to define the isocenter. Two additional bbs were placed on two phantom surfaces in order to define a spatial location of 1.5 cm anterior, 1.5 cm inferior, and 1.5 cm right from the isocenter. An axial scan of the phantom was acquired from a multislice CT simulator. The phantom was set at the linac's isocenter (lasers); either AP MV/R Lat kV images or CBCT images were taken for 2D/2D or 3D/3D matching, respectively. For 2D/2D, the accuracy of each device's isocenter was obtained by checking the distance between the central bb and the digital graticule. Then the central bb in orthogonal DRRs was manually moved to overlay to the off-axis bbs in kV/MV images. For 3D/3D, CBCT was first matched to planCT to check the isocenter difference between the two CTs. Manual shifts were then made by moving CBCT such that the point defined by the two off-axis bbs overlay to the central bb in planCT. (PlanCT can not be moved in the current version of OBI1.4.) The manual shifts were then applied to remotely move the couch. The room laser was used to check the accuracy of the couch movement. For Trilogy (or Ix-21) linacs, the coincidence of imager and linac's isocenter was better than 1 mm (or 1.5 mm). The couch shift accuracy was better than 2 mm.

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Radiation Oncology

Jin, R., J. Rock, J. Y. Jin, N. Janakiraman, J. H. Kim, B. Movsas and S. Ryu (2009). "Single fraction spine radiosurgery for myeloma epidural spinal cord compression." J Exp Ther Oncol **8**(1): 35-41. [Article Request Form](#)

Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI 48202, USA.

Radiosurgery delivers highly focused radiation beams to the defined target with high precision and accuracy. It has been demonstrated that spine radiosurgery can be safely used for treatment of spine metastasis with rapid and durable pain control, but without detrimental effects to the spinal cord. This study was carried out to determine the role of single fraction radiosurgery for epidural spinal cord compression due to multiple

myeloma. A total of 31 lesions in 24 patients with multiple myeloma, who presented with epidural spinal cord compression, were treated with spine radiosurgery. Single fraction radiation dose of 10-18 Gy (median of 16 Gy) was administered to the involved spine including the epidural or paraspinal tumor. Patients were followed up with clinical exams and imaging studies. Median follow-up was 11.2 months (range 1-55). Primary endpoints of this study were pain control, neurological improvement, and radiographic tumor control. Overall pain control rate was 86%; complete relief in 54%, and partial relief in 32% of the patients. Seven patients presented with neurological deficits. Five patients neurologically improved or became normal after radiosurgery. Complete radiographic response of the epidural tumor was noted in 81% at 3 months after radiosurgery. During the follow-up time, there was no radiographic or neurological progression at the treated spine. The treatment was non-invasive and well tolerated. Single fraction radiosurgery achieved an excellent clinical and radiographic response of myeloma epidural spinal cord compression. Radiosurgery can be a viable treatment option for myeloma epidural compression.

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Radiation Oncology

Li, S., Y. Liu, Q. Chen and J. Jin (2009). "Cord dose specification and validation for stereotactic body radiosurgery of spine." Med Dosim **34**(4): 285-92. [Article Request Form](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA. Shidong.Li@thus.temple.edu

Effective dose to a portion of the spinal cord in treatment segment, rather than the maximum point dose in the cord surface, was set as the dose limit in stereotactic-body radiosurgery (SBRS) of spine. Such a cord dose specification is sensitive to the volume size and position errors. Thus, we used stereotactic image guidance to minimize phantom positioning errors and compared the results of a 0.6-cm(3) Farmer ionization chamber and a 0.01-cm(3) compact ionization chamber to determine the detector size effect on 9 SBRS cases. The experimental errors ranging from 2% to 7% were estimated by the deviation of the mean dose in plans to the chamber with spatial displacements of 0.5 mm. The mean and measured doses for the large chamber to individual cases were significantly (approximately 17%) higher than the doses with the compact chamber placed at the same point. Our experimental results shown that the mean doses to the volume of interest could represent the measured cord doses. For the 9 patients, the mean doses to 10% of the cord were about 10 Gy, while the maximum cord doses varied from 11.6 to 17.6 Gy. The mean dose, possibly correlated with the cord complication, provided us an alternative and reliable cord dose specification in SBRS of spine.

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Radiation Oncology

Movsas, B., J. Moughan, L. Sarna, C. Langer, M. Werner-Wasik, N. Nicolaou, R. Komaki, M. Machtay, T. Wasserman and D. W. Bruner (2009). "Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801." J Clin Oncol **27**(34): 5816-22. [PDF Full-Text](#)

Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI 48202, USA. bmovsas1@hfhs.org

PURPOSE: To determine the added value of quality of life (QOL) as a prognostic factor for overall survival (OS) in patients with locally advanced non-small-cell lung cancer (NSCLC) treated on Radiation Therapy Oncology Group RTOG-9801. **PATIENTS AND METHODS:** Two hundred forty-three patients with stage II/IIIAB NSCLC received induction paclitaxel and carboplatin (PC) and then concurrent weekly PC and hyperfractionated radiation (to 69.6 Gy). Patients were randomly assigned to amifostine (AM) or no AM during chemoradiotherapy. The following pretreatment factors were analyzed as prognostic factors for OS: Karnofsky performance status, stage, sex, age, race, marital status, histology, tumor location, hemoglobin, tobacco use, treatment arm (AM v no AM) and QOL scores (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 [QLQ-C30] and Lung Cancer 13 [LC-13]). A multivariate (MVA) Cox proportional hazards model was performed using a backwards selection process. **RESULTS:** Of the 239 analyzable patients, 91% had a baseline global QOL score. Median follow-up time was 59 months for patients still alive and 17 months for all patients. Median baseline QLQ-C30 global QOL score was 66.7 on both treatment arms. Whether the global QOL score was treated as a dichotomized variable (based on the median score) or a continuous variable, all other variables fell out of the MVA for OS. Patients with a global QOL score less than 66.7 had an approximately 70% higher rate of death than patients with scores \geq 66.7 ($P = .004$). A 10-point higher baseline global QOL score corresponded to a decrease in the hazard of death by approximately 10% ($P = .004$). The other independent QOL predictors for OS were the QLQ-C30 physical

functioning ($P = .011$) and LC-13 dyspnea scores ($P = .012$). **CONCLUSION:** In this analysis, baseline global QOL score replaced known prognostic factors as the sole predictor of long-term OS for patients with locally advanced NSCLC.

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Radiation Oncology

Siddiqui, F., D. R. Ibrahim, I. Aref, M. Lu, W. S. Kim, D. Schultz and M. A. Elshaikh (2009). "Clinical outcome of pathologic Stage IIA endometrial adenocarcinoma after intravaginal brachytherapy alone." *Brachytherapy* **8**(4): 396-400. [Article Request Form](#)

[Siddiqui, Farzan; Ibrahim, Dina R.; Aref, Ibrahim; Elshaikh, Mohamed A.] Henry Ford Hosp, Dept Radiat Oncol, Detroit, MI 48202 USA. [Lu, Mei] Henry Ford Hosp, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA. [Kim, Woo Shin] Henry Ford Hosp, Dept Gynecol Oncol, Detroit, MI 48202 USA. [Schultz, Daniel] Henry Ford Hosp, Dept Pathol, Detroit, MI 48202 USA. Elshaikh, MA, Henry Ford Hosp, Dept Radiat Oncol, 2799 W Grand Blvd, Detroit, MI 48202 USA. melshai1@hfhs.org

PURPOSE: We studied the impact of different prognostic factors on the clinical outcome for the patients with pathologic Stage IIA endometrial adenocarcinoma who had surgical staging (SS) and received adjuvant high-dose-rate intravaginal brachytherapy (IVB) alone. **METHODS AND MATERIALS:** Sixty-one patients with Stage IIA endometrial adenocarcinoma were retrospectively studied. Cox proportional hazards regression was used to study prognostic factors. **RESULTS:** All the patients underwent SS between July 1994 and December 2005. The median age was 64 years (range, 46-71 years). The median number of lymph nodes sampled was 8 (range, 7-12). All the patients received adjuvant IVB to doses of 35-36 Gy in four to five fractions prescribed to the surface. The myometrial invasion was $<50\%$ in 33 patients and $\geq 50\%$ for 28 patients. The lymphovascular invasion (LVI) and the lower uterine segment involvement were identified in 18% and 61%, respectively. At a median followup of 64 months (range, 8-153 months), there were 7 patients who developed recurrences. On univariate analysis, the only factor significantly predictive for locoregional recurrence was LVI ($p = 0.01$). In regard to overall survival (OS), factors that were significantly predictive on univariate analysis were LVI ($p = 0.03$), tumor grade ($p = 0.04$), and depth of myometrial invasion ($p = 0.04$). The 5-year rates of vaginal and pelvic recurrences were 1.7% and 8.2%, respectively. The 5-year local control and OS rates were both 87%. **CONCLUSIONS:** Our results suggest excellent local control with adjuvant IVB alone for selected patients with Stage IIA endometrial adenocarcinoma. The patients with positive LVI and deep myometrial invasion have a worse locoregional control and OS despite SS and adjuvant IVB. (c) 2009 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

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Sleep Medicine

Czeisler, C. A., J. K. Walsh, K. A. Wesnes, S. Arora and T. Roth (2009). "Armodafinil for Treatment of Excessive Sleepiness Associated With Shift Work Disorder: A Randomized Controlled Study." *Mayo Clinic Proceedings* **84**(11): 958-972. [PDF Full-Text](#)

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OBJECTIVE: To assess the effect of armodafinil, 150 mg, on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic (≥ 3 months) shift work disorder (SWD) of moderate or greater severity. **PATIENTS AND METHODS:** This 12-week, randomized controlled study was conducted at 42 sleep research facilities in North America from April 2 through December 23, 2004, and enrolled 254 permanent or rotating night shift workers with SWD. Entry criteria included excessive sleepiness during usual night shifts for 3 months or longer (corroborated by mean sleep latency of 56 minutes on a Multiple Sleep Latency Test), insomnia (sleep efficiency $\leq 87.5\%$ during daytime sleep), and SWD that was judged clinically to be of moderate or greater severity. Patients received armodafinil, 150 mg, or placebo 30 to 60 minutes before each night shift. Physiologic sleep propensity during night shift hours, clinical Impression of severity, patient-reported sleepiness, and cognitive function were assessed during laboratory night shifts at weeks 4, 8, and 12. **RESULTS:** Armodafinil significantly improved

mean (SD) sleep latency from 2.3 (1.6) minutes at baseline to 5.3 (5.0) minutes at final visit, compared with a change from 2.4 (1.6) minutes to 2.8 (2.9) minutes in the placebo group ($P < .001$). Clinical condition ratings Improved in more patients receiving armodafinil (79%) vs placebo (59%) ($P = .001$). As reported by patients' diaries, armodafinil significantly reduced sleepiness during laboratory nights ($P < .001$), night shifts at work ($P < .001$), and the commute home ($P = .003$). Armodafinil Improved performance on standardized memory ($P < .001$) and attention (power, $P = .001$; continuity, $P < .001$) tests compared with placebo. Armodafinil was well tolerated and did not affect daytime sleep, as measured by polysomnography. **CONCLUSION:** In patients with excessive sleepiness associated with chronic SWD of moderate or greater severity, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency above the level considered to indicate severe sleepiness during the daytime. Armodafinil also significantly improved measures of overall clinical condition, long-term memory, and attention.

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Sleep Medicine

Palesh, O. G., J. A. Roscoe, K. M. Mustian, T. Roth, J. Savard, S. Ancoli-Israel, C. Heckler, J. Q. Purnell, M. C. Janelsins and G. R. Morrow (2009). "Prevalence, Demographics, and Psychological Associations of Sleep Disruption in Patients With Cancer: University of Rochester Cancer Center-Community Clinical Oncology Program." *J Clin Oncol* **EPub Ahead of Print**. [PDF Full-Text](#)

University of Rochester, Rochester, NY; Henry Ford Hospital, Detroit, MI; Universite Laval, Quebec City, Quebec, Canada; University of California San Diego, San Diego, CA; and Washington University, St Louis, MO.

PURPOSE: Sleep disruption is prevalent in patients with cancer and survivors, but the prevalence of insomnia, a distressing sleep disorder, in these populations has yet to be determined in large-scale studies. **PATIENTS AND METHODS:** A total of 823 patients with cancer receiving chemotherapy (mean age, 58 years; 597 female patients) reported on sleep difficulties in a prospective study. **RESULTS:** During day 7 of cycle 1 of chemotherapy, 36.6% ($n = 301$) of the patients with cancer reported insomnia symptoms, and 43% ($n = 362$) met the diagnostic criteria for insomnia syndrome. Patients with cancer younger than 58 years were significantly more likely to experience either symptoms of insomnia or insomnia syndrome ($\chi^2 = 13.6$; $P = .0002$). Patients with breast cancer had the highest number of overall insomnia complaints. A significant positive association was found between symptoms of insomnia during cycles 1 and 2 of chemotherapy ($\phi = .62$, $P < .0001$), showing persistence of insomnia during the first two cycles of chemotherapy. Sixty percent of the patient sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (all $P < .0001$). **CONCLUSION:** The proportions of patients with cancer in this sample reporting symptoms of insomnia and meeting diagnostic criteria for insomnia syndrome during chemotherapy are approximately three times higher than the proportions reported in the general population. Insomnia complaints persist throughout the second chemotherapy cycle for the majority of patients with cancer in this study. Insomnia is prevalent, underrecognized, undermanaged, and understudied among patients with cancer receiving chemotherapy.

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Sleep Medicine

Randall, S., C. E. Johanson, M. Tancer and T. Roehrs (2009). "Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: a preliminary study." *Sleep* **32**(11): 1513-9. PMC2768958. [PDF Full-Text](#)

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STUDY OBJECTIVE: 3,4-Methylenedioxymethamphetamine (MDMA) affects monoamine neurotransmitters that play a critical role in sleep and daytime alertness. However, the acute effects of MDMA on sleep and daytime sleepiness have not been studied under placebo-controlled conditions. This study was designed to establish the effects of acute MDMA or placebo administration and sleep restriction on sleep and daytime sleepiness. **DESIGN:** Participants with a history of MDMA use were studied on 3 sessions of 3 nights (baseline, treatment, and recovery) and 2 days (following night 2 and 3) per session. On treatment nights (night 2), participants received placebo or 2 mg/kg of MDMA or underwent a restricted bed schedule with placebo. Sleep restriction was a positive control to compare sleep loss and consequent sleepiness associated

with MDMA use. The scheduled sleep period was 8 hours long on nonrestricted nights, and standard sleep recordings and daytime sleepiness tests were conducted. Age-matched controls received 1 night and day of standard sleep and daytime sleepiness testing. SETTING: Sleep laboratory. PARTICIPANTS: Seven recreational MDMA-users and 13 matched control subjects. MEASUREMENTS AND RESULTS: Acute MDMA shortened sleep primarily by increasing sleep latency, and it reduced stage 3/4 sleep and suppressed rapid eye movement (REM) sleep. The MDMA-reduced sleep time was not associated with increased daytime sleepiness the following day, as was seen in the sleep-restriction condition. Compared with control subjects, the MDMA users on the first night in the laboratory had shorter total sleep times and less stage 3/4 sleep. Average daily sleep latency on daytime sleepiness tests the day after nighttime placebo administration was increased in MDMA users compared with the control subjects, and MDMA users had an elevated number of sleep-onset REM periods on these tests, compared with control subjects. CONCLUSIONS: Acute MDMA administration disrupts sleep and REM sleep, specifically, without producing daytime sleepiness such as sleep restriction does. Compared with control subjects, recreational MDMA users showed evidence of hyperarousal and impaired REM function. The mechanism behind these effects is likely due to the deleterious effects of MDMA on catecholamines.

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Surgery

France, E. and V. Velanovich (2009). "The relative influence of surgical disease and comorbidities on patient responses to a generic health-related quality-of-life instrument." Am Surg **75**(11): 1084-90. [PDF Full-Text](#)

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Generic health-related quality-of-life (QoL) instruments are increasingly used to assess the outcomes of surgical interventions. However, it is unclear to what extent the patient's associated comorbidities have on the responsiveness of these instruments to measure changes caused by the operation. The purpose of this study was to assess the relative influence of comorbidities to surgical disease in how patients answered the items of the most frequently used generic instrument, the SF-36. Sixty-nine preoperative patients completed the SF-36, which contains 36 items covering eight domains and a health transition question. For each of the 36 items, patients were asked to rate the influence of their surgical disease and their comorbidities on how they answered the items from 1 to 10. The surgical disease, comorbidities, and medications were recorded. Data was analyzed using the Mann-Whitney U test and linear regression analysis. Of the 36 items of the SF-36, patients reported that their surgical disease influences nine items greater than their comorbidities ($P < 0.05$). Using linear regression analysis, the number of comorbidities did not effect the influence of the surgical disease in any item; however, this number had a direct relationship ($P < 0.05$) with the influence of comorbidities on how the patient answered the item. However, the magnitude of the influence was low. There was an inverse (negative slope, $P < 0.05$) relationship between the number of comorbidities and the score of six of eight domains. Although the surgical disease has more of an influence on how patients answered the items of the SF-36, as the number of comorbidities increased, these seem to have more influence. Therefore, the SF-36 would be a good choice for assessing QoL in most surgical disease. However, as the overall magnitude of this influence was low, this may be a cause of the lack of responsiveness of generic QoL instruments in measuring the effect of operations on QoL. Importantly, as the number of comorbidities increased, the scores of the SF-36 decreased, implying that the effect of the surgical disease would be greater in patients with fewer comorbidities.

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Surgery

Fregene, A., X. L. Jing, L. A. Monson and S. R. Buchman (2009). "Alteration in Volumetric Bone Mineralization Density Gradation Patterns in Mandibular Distraction Osteogenesis following Radiation Therapy." Plast Reconstr Surg **124**(4): 1237-44. [PDF Full-Text](#)

Ann Arbor and Detroit, Mich. From the University of Michigan Medical School and the Henry Ford Medical Center.

BACKGROUND:: The use of mandibular distraction osteogenesis for tissue replacement after oncologic resection or for deformations secondary to radiotherapy could have immense therapeutic ramifications. Radiotherapy, however, drastically impairs bone healing, potentially precluding the use of mandibular distraction osteogenesis as a durable reconstructive option. The authors have previously demonstrated

significantly decreased mechanical and histologic metrics of the mandibular distraction osteogenesis regenerate after 36 Gy. The authors' goal is to now investigate the effect of these same radiation dosages on bone densitometrics using micro-computed tomographic scanning. METHODS:: Six Sprague-Dawley rats received 36-Gy fractionated radiotherapy sessions to the left mandible; six received none. All animals had external fixators placed, creation of osteotomies, distraction, and consolidation. Mandibles were scanned with micro-computed tomographic scanning. Volumetric density and microdensitometric measurements were analyzed. RESULTS:: There was a significant difference in volumetric bone mineralization patterns in irradiated animals. Bone volume fraction and bone mineral density, however, demonstrated no significant differences. CONCLUSIONS:: The authors discovered a significant increase of low mineralized, immature bone and a significant decrease of highly mineralized, mature bone in the irradiated regenerate. These findings corroborate the authors' hypothesis that radiation induces a diminution in cell function, impairing optimal bone regeneration. Overall densitometrics, however, were unchanged according to micro-computed tomographic measurements, despite documented significant changes in biomechanical and histologic metrics. An optimal radiation dose must now be sought that demonstrates a higher degree of reproducible degradation, but not irreversible destruction, in all three outcomes. Such an approach will allow formulation of therapeutic interventions designed to enhance mandibular distraction osteogenesis so that it may be used as a viable reconstructive option.

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Surgery

Kakkos, S. K., J. C. Lin, J. Sparks, M. Telly, M. McPharlin and D. J. Reddy (2009). "Prospective Comparison of the Pneumatic Cuff and Manual Compression Methods in Diagnosing Lower Extremity Venous Reflux." Vascular and Endovascular Surgery **43**(5): 480-484. [Article Request Form](#)

[Kakkos, Stavros K.; Lin, Judith C.; Sparks, Jennifer; Telly, Melissa; McPharlin, Michalene; Reddy, Daniel J.] Henry Ford Hosp, Div Vasc Surg, Dept Surg, Detroit, MI 48202 USA.

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Aim: To compare pneumatic cuff with manual compression in diagnosing reflux in patients with chronic venous insufficiency (CVI). Patients and Methods: Eighteen patients (Clinical Etiologic Anatomic Pathophysiologic [CEAP 2-5], median Venous Clinical Severity Score [VCSS 6.5]) were studied. The VenaPulse device (ACI Medical, San Marcos, California) was used for cuff inflation. The hemodynamic performance of the 2 methods was tested in the first 9 patients, while their diagnostic value was tested in the last 9 patients. Results: Both methods induced equal compression with median peak velocity of the antegrade flow (PVA) being 86 cm/s ($P = .65$). Coefficient of variation (CV) for PVA in the superficial veins was significantly higher with the manual method (16.8%) compared to the VenaPulse method (9.5%, $P < .001$), while sensitivity and specificity were 85% and 100%, and 78% (kappa .68, $P < .001$) and 100%, respectively. Conclusions: Pneumatic cuff and manual compression were shown to be equally effective in diagnosing venous reflux. Cost-effectiveness and ease-of-use studies comparing these methods are justified.

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Surgery

Rubinfeld, I., C. Thomas, S. Berry, R. Murthy, N. Obeid, O. Azuh, J. Jordan and J. H. Patton (2009). "Octogenarian abdominal surgical emergencies: not so grim a problem with the acute care surgery model?" J Trauma **67**(5): 983-9. [PDF Full-Text](#)

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BACKGROUND: As the aging population continues to increase, the surgical needs of the elderly will increase. The acute care surgery model has been developed in which the trauma team also manages all general surgical emergencies to improve patient outcomes. We retrospectively reviewed our elderly acute care surgery population during the past 5 years to determine the variables affecting major abdominal surgery outcomes. METHODS: Patients aged 80 years and older who received an emergent major abdominal operation by our Acute Care Surgery team between July 2000 and November 2006 were included. We assessed after-hours operations, length of stay, duration of operation, gender, comorbidities, and mortality. Administrative, operating room, and corporate databases were used for demographics, comorbidities, admission logistics, American Society of Anesthesiologists (ASA) score, and mortality. We performed SPSS, chi2, and logistic regression

analyses. RESULTS: A total of 183 operations were performed with a mortality of 15%. Significant predictors were ASA score and female gender, with increasing ASA scores leading to worse outcomes and women faring worse than men as an independent variable. Neither operative duration nor off-hours surgery was associated with increased mortality. CONCLUSIONS: This is the first study to report mortality data and expected survival curves for major abdominal surgery in the octogenarian population. Our data prove that it is safer than previously thought to operate on the elderly. Our mortality data and survival curves provide real data for the surgeon to be able to risk stratify and discuss predicted outcomes with consultants, patients, and families.

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Surgery

Velanovich, V., I. Rubinfeld, J. H. Patton, J. Ritz, J. Jordan and S. Dulchavsky (2009). "Implementation of the National Surgical Quality Improvement Program: Critical Steps to Success for Surgeons and Hospitals." [American Journal of Medical Quality](#) **24**(6): 474-479.

[Article Request Form](#)

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The National Surgical Quality Improvement Program (NSQIP), as administered by the American College of Surgeons, became available to private sector hospitals across the United States in 2004. The program works to improve surgical outcomes by providing high-quality, risk-adjusted data to surgeons at a given hospital to stimulate discussion and define target areas for improvement. Although the NSQIP began in the early 1990s with Veterans Administration hospitals and expanded to private sector hospitals nearly 5 years ago, the "how to" process for NSQIP implementation has been left to individual institutions to manage on their own. The NSQIP was instituted at a large tertiary hospital in 2005, identifying through experience 12 critical steps to help surgeons and hospitals implement the NSQIP. (Am J Med Qual 2009;24:474-479)

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Urology

Badani, K. (2009). "Untitled." [Bju International](#) **104**(11): 1720-1721. [Article Request Form](#)

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Urology

Krane, L. S., M. Bhandari, J. O. Peabody and M. Menon (2009). "Impact of percutaneous suprapubic tube drainage on patient discomfort after radical prostatectomy." [Eur Urol](#) **56**(2): 325-30. [PDF Full-Text](#)

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BACKGROUND: Patients undergoing radical prostatectomy (RP) traditionally require urethral catheterization for adequate bladder drainage in the postoperative period. However, many patients have significant discomfort from the urethral catheter. OBJECTIVE: To describe a technique of percutaneous suprapubic tube (PST) bladder drainage after robotic-assisted laparoscopic radical prostatectomy (RALP) and to evaluate patient discomfort, complications, continence, and stricture rate after this procedure. DESIGN, SETTING, AND PARTICIPANTS: Two hundred two patients undergoing RALP were drained with a 14F PST instead of a urethral catheter. The PST was placed robotically at the conclusion of the urethrovesical anastomosis and secured to the skin over a plastic button. Beginning on postoperative day 5, patients clamped the PST, urinated per urethra, and measured the postvoid residual (PVR) drained by PST. The PST was removed when residuals were <30 cm(3) per void. The control group consisted of 50 consecutive patients undergoing RALP with urethral catheter drainage. MEASUREMENTS: The primary end point was catheter-associated discomfort as measured with the Faces Pain Score-Revised (FPS-R). Secondary end points included use of anticholinergics, complications related to the PST, urinary continence, and urethral stricture. RESULTS AND LIMITATIONS: When compared with urethral catheter patients, PST patients had significantly decreased

catheter-related discomfort on postoperative days 2 and 6 ($p < 0.001$). Anticholinergic medication was required by one PST and four urethral catheter patients ($p < 0.001$). Ten patients required urethral catheterization for PST dislodgement ($n = 5$) or urinary retention ($n = 5$). No patient has developed a urethral stricture at a mean follow-up of 7 mo. **CONCLUSIONS:** PST provides adequate urinary drainage following RALP with less patient discomfort and no increased risk of urethral stricture.

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Urology

Sarveswaran, S., C. E. Myers and J. Ghosh (2009). "MK591, a leukotriene biosynthesis inhibitor, induces apoptosis in prostate cancer cells: Synergistic action with LY294002, an inhibitor of phosphatidylinositol 3'-kinase." **Cancer Lett Epub Ahead of Print.** [Article Request Form](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI 48202, United States.

MK591 is a synthetic compound which specifically inhibits the activity of 5-Lox and is currently under development for the treatment of asthma. We observed that human prostate cancer cells treated with MK591 undergo apoptosis within hours of treatment. Apoptosis involves severe morphological alteration, externalization of phosphatidyl-serine, cleavage of PARP, and degradation of chromatin-DNA. MK591 also induced rapid activation of the stress kinase, c-Jun N-terminal kinase (JNK), which plays an important role in the apoptosis process. The phosphatidylinositol 3'-kinase-Akt/protein kinase B (PI3K/Akt) axis is a well-known pro-survival pathway which prevents apoptosis through defined anti-apoptotic mechanisms in a variety of cancer cells. Interestingly, we observed that MK591 triggers apoptosis in prostate cancer cells without inhibition of PI3K-Akt, or ERK. Moreover, it was observed that MK591 and LY294002 (an inhibitor of PI3K) exert synergistic effect in inducing apoptosis in prostate cancer cells. Altogether, these findings indicate that 5-Lox inhibition-induced apoptosis in prostate cancer cells occurs without inhibition of PI3K-Akt, or ERK, and suggest for the existence of an Akt- and ERK-independent survival mechanism(s) in these cancer cells maintained via signals generated by metabolites of 5-Lox.

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Urology

Siddiqui, S. A., L. S. Krane, A. Bhandari, M. N. Patel, C. G. Rogers, H. Stricker, J. O. Peabody and M. Menon (2009). "The Impact of Previous Inguinal or Abdominal Surgery on Outcomes After Robotic Radical Prostatectomy." **Urology Epub Ahead of Print.** [PDF Full-Text](#)

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

OBJECTIVES: To evaluate our experience with robotic radical prostatectomy (RRP) in the setting of previous inguinal or abdominal surgery. **METHODS:** From a prospective cohort of 3950 consecutive patients who underwent transperitoneal RRP between September 2001 and September 2008, we identified 1049 (27%) patients with a history of abdominal or inguinal surgery. Demographic data including body mass index, age at the time of surgery, serum prostate-specific antigen, and clinical stage were prospectively recorded. Clinical endpoints measured included estimated blood loss (EBL), console time, total operative time, and perioperative complications. Degree of adhesiolysis at the time of surgery was graded into minor, moderate, or large. **RESULTS:** In comparing patients with previous abdominal or inguinal surgery with no surgery, there were no differences in EBL (150 vs 151 mL, $P = .79$), total operative time (158 minutes v second 155 minutes, $P = .15$), body mass index (27.8 vs 27.4, $P = .2$), preoperative prostate-specific antigen (6.1 vs 6.3, $P = .07$) and clinical stage ($P = .71$). A total of 243 (24%) of patients with previous surgery required adhesiolysis vs 246 (8%) of patients with no previous surgery ($P < .001$). Appendectomy was the most common previous surgery identified (11%). Patients with a previous history of colectomy had the highest incidence of adhesiolysis (72%). A total of 5 bowel injuries were recorded in the cohort of 3950 patients; of these 3 patients had a history of prior abdominal surgery. **CONCLUSIONS:** Previous abdominal or inguinal surgery is not a contraindication to RRP. The majority of these patients can have their procedure safely performed without an increased risk of complications.

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Urology

Thamilselvan, V., M. Menon and S. Thamilselvan (2009). "Oxalate-induced activation of PKC-alpha and -delta regulates NADPH oxidase-mediated oxidative injury in renal tubular epithelial cells." *Am J Physiol Renal Physiol* **297**(5): F1399-410. [PDF Full-Text](#)

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Oxalate-induced oxidative stress contributes to cell injury and promotes renal deposition of calcium oxalate crystals. However, we do not know how oxalate stimulates reactive oxygen species (ROS) in renal tubular epithelial cells. We investigated the signaling mechanism of oxalate-induced ROS formation in these cells and found that oxalate significantly increased membrane-associated protein kinase C (PKC) activity while at the same time lowering cytosolic PKC activity. Oxalate markedly translocated PKC-alpha and -delta from the cytosol to the cell membrane. Pretreatment of LLC-PK1 cells with specific inhibitors of PKC-alpha or -delta significantly blocked oxalate-induced generation of superoxide and hydrogen peroxide along with NADPH oxidase activity, LDH release, lipid hydroperoxide formation, and apoptosis. The PKC activator PMA mimicked oxalate's effect on oxidative stress in LLC-PK1 cells as well as cytosol-to-membrane translocation of PKC-alpha and -delta. Silencing of PKC-alpha expression by PKC-alpha-specific small interfering RNA significantly attenuated oxalate-induced cell injury by decreasing hydrogen peroxide generation and LDH release. We believe this is the first demonstration that PKC-alpha- and -delta-dependent activation of NADPH oxidase is one of the mechanisms responsible for oxalate-induced oxidative injury in renal tubular epithelial cells. The study suggests that the therapeutic approach might be considered toward attenuating oxalate-induced PKC signaling-mediated oxidative injury in recurrent stone formers.