

## Poster #12

### ***Weekend Nationwide Analysis Admissions Predict Higher Mortality in Patients with Atrial Fibrillation***

Abhishek Deshmukh, Sadip Pant, Gagan Kumar Zoran Bursac, Hakan Paydak, Jawahar L. Mehta

**Introduction:** Atrial Fibrillation (AF) is the most common sustained cardiac rhythm disturbance, affecting an estimated 2.5 million people in the United States. It is now increasingly recognized that the presence of AF is an independent contributor to mortality, morbidity and impaired quality of life. Previous studies have identified a “weekend effect” in outcomes of patients with various acute medical conditions admissions. The aim of our study was to investigate if weekend admissions for AF have worse outcomes compared with those admitted on weekdays in a real world nationwide cohort.



**Methods:** This was a cross sectional study using the Nationwide Inpatient Sample (NIS) 2008 database. A total of 86,497 discharges with AF as primary discharge diagnosis were identified with appropriate International Classification of Diseases, IX edition codes. Admission was considered to be a weekend admission if the patient was admitted between midnight Friday through midnight Sunday. In-hospital mortality, length of stay ( LOS ) and cardioversion procedures were recorded.

**Results:** Of the total discharges with primary diagnosis of AF, 19.6% were admitted on weekend. Among patients admitted on weekend 1.1% died in hospital compared to 0.9% among those admitted during week. The proportion receiving cardioversion procedures used for AF on weekends were lower as compared to weekdays (7.9% vs. 16.2% respectively;  $p < 0.0001$ ). After adjusting for patient characteristics, hospital characteristics and disease severity, the adjusted in-hospital mortality odds were higher for weekend admissions (OR=1.23, 95% CI=1.03-1.51;  $p < 0.0001$ ). The weekend admissions were associated with significantly lower odds of cardioversion procedures (OR=0.5, 95% CI=0.45-0.55,  $p < 0.0001$ ). The LOS was significantly longer for weekend admissions .

**Conclusions:** Patients admitted with AF on weekends have increased mortality and lower use of cardioversion procedures. Further research needs to be done to investigate the reasons behind worse outcomes for weekend admissions.

# UAMS



COLLEGE OF MEDICINE

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

## UAMS College of Medicine Series Showcase of Medical Discoveries:

A focus on  
Cardiovascular Research



*A wine and cheese reception featuring  
UAMS investigators discussing their  
research and discoveries.*

Winthrop P. Rockefeller Cancer Institute Rotunda

Wednesday, November 28, 2012

4:00—5:30 p.m.

## Poster #1

### ***Can we Improve Kidney Function Prior to Kidney Transplant?***

LeeAnn MacMillan Crow, Nirmala Parajuli, Akira Marine

Over 100,000 Americans with kidney failure are currently on waiting lists for kidney transplants. However, last year only ~17,000 kidney transplants were performed. Thus, there clearly is a significant kidney demand/supply imbalance. Placing donor kidneys in cold solution preserves the kidney and allows time to match the donor kidney to a suitable recipient. However, our laboratory and others have demonstrated that kidneys placed in cold storage solution are injured. Thus, one goal of our laboratory is to identify the mechanisms by which injury occurs and test new therapies to prevent injury, so we can improve the quality and availability of donor kidneys for transplant. Currently, many kidneys are discarded after cold storage since there is no reliable test to assess kidney quality. Therefore, another of our goals is to evaluate if a method we devised to assess the health of mitochondria in cold stored kidneys could be used clinically to assess donor kidneys. We recently reported that a drug called Mitoquinone (or MitoQ) can prevent injury to kidneys placed in cold storage solution. We plan to test the impact that MitoQ has on kidney function following transplant.



## Poster #2

### ***Predicting Heart Attacks in Women: Recognizing Early Symptoms***

Jean McSweeney, Mario Cleves, Ellen Fischer, Martha Rojo, Christina Pettey



**BACKGROUND:** Coronary heart disease (CHD) kills over 240,000 women in the U. S. annually. There is agreement that under-recognition of women's symptoms and difficulty in diagnosing their heart disease contribute to their greater disability and mortality. Coronary heart disease is treatable if detected early yet few questionnaires measure women's early warning prodromal symptoms (PS) of CHD. Many women report little or no chest pain prior to or during a heart attack. Thus, it is vital to identify women's

symptoms other than chest pain associated with heart disease. However, no questionnaires assess other CHD prodromal symptoms that women report. The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS) assesses 30 symptoms, weighted by severity and frequency; the scores are summed to create an overall symptom score.

**PURPOSE:** To assess the ability of the MAPMISS to predict women's CHD events and to identify the most predictive symptoms.

**METHODS:** Women without heart disease referred to cardiologists in Arkansas participated. The MAPMISS questionnaire was administered to 1,097 women every 3 months for 2 years.

**RESULTS:** The prodromal score and symptoms were predictive of an event. Five symptoms were significantly associated with increased risk: discomfort in jaws/teeth, unusual fatigue, arm discomfort, shortness of breath and generalized chest discomfort. Women reporting 1 or more of these symptoms were 4 times as likely to suffer a cardiac event.

**CONCLUSIONS:** Both the MAPMISS PS scores and number of PS were significantly associated with cardiac events, suggesting specific symptoms can be easily assessed using the MAPMISS. This questionnaire could provide a predictive screen to assist clinicians in recognizing heart disease in women earlier.

## Poster #11

### ***Upregulation of MicroRNAs 21 and 223 in an Animal Model of Pulmonary Hypertension***

Igor Gubrij, Amanda. Pangle, Li Pang, Larry G. Johnson

**Rationale:** MicroRNAs (miRs) are small ribonucleic acid (RNA) molecules 21-22 base pairs in size that block the function of genes by binding to the messenger (m) RNA, the RNA that codes for proteins, to degrade the mRNA or block the formation of proteins. MiRs are found in a variety of human tissues and play pivotal roles in the control of cell growth, differentiation, and programmed cell death (apoptosis). MiRs have been detected in microscopic lesions of specimens from patients with pulmonary hypertension (PH), a disease affecting the blood vessels in the lungs and the function of the right side of the heart. However, which miRs are found in the lung or its blood vessels and their functions are incompletely understood. We sought to identify miRs that might be important for patients with PH by examining miRs in different tissue types from animals that have a form of PH similar to humans.



**Methods:** We isolated the RNA from the right ventricular (RV) tissue of rats treated with the drug monocrotaline (MCT, 60 mg/kg), which causes PH in rats, and also isolated RNA from rats injected with saline or salt solution. The RNA was placed on a slide or chip (microarray) with a large number of known miRs, and at least two miRs showed higher levels in the RV of MCT rats compared to saline rats. Subsequently, we compared right ventricular systolic pressure (RVSP) between MCT and saline rats, and then the heart and lungs were removed and the pulmonary arteries (PA) were dissected out with a microscope. RNA was isolated from the lungs, PA, RV of the heart, and from the plasma of blood samples. Quantitative polymerase chain reaction (PCR) assays were used to measure the relative amounts of these two microRNAs.

**Results:** MicroRNA microarray analysis suggested that miRs 21 and 223 were increased in the RV of MCT-treated rats. Development of PH in MCT rats was associated with a 4-fold increase in lung miR-21 levels and a 2-fold increase in lung miR-223 levels relative to saline treated rats. Differences in levels or amounts of microRNAs were also detected in PA of MCT-rats (miR-21, 6-fold greater; miR-223, 2.5-fold greater). In the RV, miR-21 was 5-fold greater and miR-223 was 4-fold greater in MCT-rats relative to controls. No differences in expression of miR-21 and miR-223 were detected in plasma. Increased levels of miR-223 in an animal model of PH has not been previously reported. Studies in other animal models of PH and in human pulmonary artery smooth muscle cells are underway.

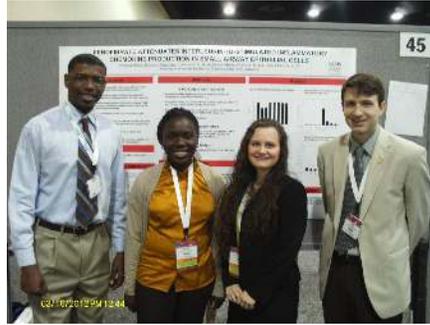
**Conclusions:** Increased levels of the microRNA miR-223 in an animal model of PH is a novel finding, whereas increased levels of miR-21 have been reported by others. These data suggest that miR-21 and miR-223 may represent potential therapeutic targets for drug development in PH. Future studies will address which pathways linked to human PH are affected by miR-223 and miR-21 and whether blocking these two miRs in MCT rats alters the development of PH. We will also test the relevance of our finding in rats in human cell models of pulmonary hypertension. Ultimately, we would also like to test these findings in human lung samples from patients with pulmonary hypertension. *Supported by a VA Merit Award (LGJ)*

### Poster #9

#### **Personalized Genomic Approaches to Enhance the Cardiovascular Health of Arkansans**

Ryan Farris, Charla Wiley, [Elvin T. Price](#)

Cardiovascular disease (CVD) is the leading cause of mortality in the USA, accounting for approximately 50% of all deaths. The prevalence of various CVDs is consistently higher among Arkansans when compared to the general population of the USA. Studies suggest that genetics and environmental factors both contribute to the increased prevalence of CVDs among Arkansans. Recently, the societal costs that are attributable to CVDs among Arkansans were characterized. The Arkansas Acute Stroke Care Task Force report of 2010 revealed that BCBS and Medicaid collectively spend \$540 million annually on the treatment of CVDs. Furthermore, data from the Milken Institute suggested that lost productivity due to hypertension alone in 2003 cost Arkansas \$3.13 billion. Moreover, this estimate is expected to rise to \$8.98 billion by 2023. Personalized genomic approaches to optimize cardiovascular health have the potential to positively impact health outcomes and to reduce the economic impact of CVD on Arkansas. Genomic tools offer the possibility of tailoring patient care based on an individual's genetic code. Our laboratory will present data showing how we use genomics to personalize medical treatment and reduce the risks of CVD.



### Poster #10

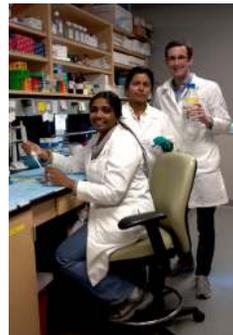
#### **Biological Mechanisms and Potential Treatments of Radiation-Induced Heart Disease**

[Marjan Boerma](#), Viji Mohanseenivasan, Preeti Tripathi, Ben Lieblong



The treatment of cancer commonly involves surgery, chemotherapy, and in more than 50% of all patients also radiation therapy. While radiation therapy leads to many cancer cures, the exposure of normal non-cancer tissues to radiation causes side effects. For instance, radiation-induced heart disease (RIHD) is one of the serious side effects of radiation therapy of tumors in the chest, such as in breast cancer, cancer of the stomach or lung cancer, when the heart is located in the field of radiation. It takes several years to decades before symptoms of RIHD appear,

but then the disease gets progressively worse. Manifestations of RIHD include enhanced hardening of the walls of blood vessels in the heart, excess scar tissue formation in the heart, and a loss of heart function. Radiation therapy techniques have improved over the last ten years in order to reduce the radiation exposure of normal tissues. However, in many cases of chest radiation therapy, exposure of the heart can still not be prevented. Biological mechanisms of RIHD are not well understood, and there is no available treatment. Our lab does pre-clinical research to understand the mechanisms of RIHD and to investigate methods by which we may treat this side effect of radiation therapy.



### Poster #3

#### **LOX-1: A Novel Target for Cardiovascular Diseases**

Sadip Pant, Dayuan Lu, Changping Hu, Jingjun Lu, Xianwei Wang, Zufeng Ding, Kottayil Varughese, Magomed Khaidakov, [Jay Mehta](#)

We first identified the presence of a new receptor of oxidized LDL cholesterol receptor LOX-1 in human coronary artery endothelial cells about a decade ago. LOX-1 is responsible for uptake, internalization and degradation of ox-LDL. It uptake initiates many of the signals for development of atherosclerosis. This receptor is upregulated in atherosclerosis, as well as in other conditions associated with oxidative stress, such as myocardial ischemia, hypertension and diabetes. We developed a mice strain in which LOX-1 is lacking. These mice lacking LOX-1 have significant less atherosclerosis, myocardial ischemia and hypertensive response to angiotensin II. Further, we identified that humans with LOX-1 single nucleotide polymorphism (SNPs) are at high risk of developing acute myocardial infarction. Currently, we are trying to develop small molecules that would block LOX-1 activity. We believe that LOX-1 directed therapy may be very useful in many cardiovascular disease states.

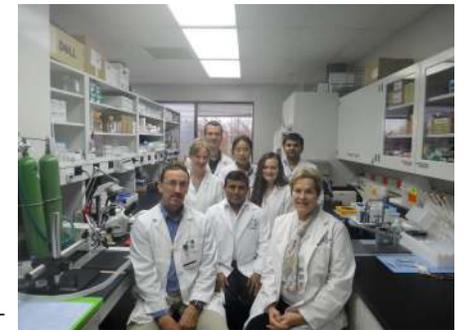


### Poster #4

#### **The TRPC3 Channel as a New Target for Antihypertensive Drug Therapy**

Asif Pathan, Brandi Bowlin, Khaled Machaca, Joel Abramowitz, Fang Zheng, [Nancy J. Rusch](#)

Canonical transient receptor potential (TRPC) channels conduct  $Ca^{2+}$  and  $Na^{+}$  into vascular smooth muscle cells (VSMCs) of arteries to cause contraction and elevate blood pressure. Thus, it has been proposed that new drugs developed to block the TRPC channels will dilate arteries and lower blood pressure. However, there are 7 subtypes of TRPC channels (TRPC1-7) and which channel subtypes are responsible for arterial contraction is unknown. Here, we compared vascular and blood pressure responses between wild-type (WT) and TRPC3 knockout (KO) mice to define the role of the TRPC3 channel subtype in arterial contraction; importantly, the TRPC3 channel was recently implicated in human hypertension. Initially, we observed that TRPC3 channels were required for the cation current and vasoconstriction of small arteries to  $\alpha_1$ -adrenergic receptor ( $\alpha_1$ -AR) activation, a stimulus implicated in hypertension. Next we observed that TRPC3 KO mice (in which the TRPC3 gene is deleted) showed less blood pressure elevation in response to stimulation of  $\alpha_1$ -AR than WT mice. Finally, we report that TRPC3 KO mice fail to fully develop hypertension in response to a chronic infusion of angiotensin II, another endogenous substance implicated in human hypertension. Thus, the TRPC3 channel may contribute to the development of acute and chronic hypertension, and pharmacological block of the TRPC3 channel may provide a new strategy to lower blood pressure in hypertensive individuals. *Supported by Grant Z01-ES101846 from the Intramural Research Program of the NIH (JA), NIH R01 HL064806 (NJR), NPRP 08-392-3-087 (NJR and KM) from the Qatar National Research Foundation and AHA 12PRE11850002 (ARP) from American Heart Association.*



## Poster #5

### **The Power of Platelets**

Jerry Ware, Judith Dent, Susan Russell, Ankit Bhargava, Adam Corken

Blood platelets are well known as major participants in blood clots causing strokes and myocardial infarcts (heart attack). The platelet has a “sticky” nature leading to platelet clumps and blood clots, but platelets also interact with other circulating blood cells. This has led to a growing recognition for platelet relevance in a wide range of diseases. For example, platelets can associate with circulating tumor cells to support metastasis. Platelets interact with blood cells and influence inflammation. As such, the platelet is in a position to affect a wide range of inflammatory diseases, such as rheumatoid arthritis and infection. These “new” roles for platelets suggest therapeutic opportunities that were not imagined even five years ago. The Ware laboratory uses a variety of mouse genetic models with non-functional platelets missing key receptor proteins in experimental models mimicking human diseases. An overview of results from our lab will illustrate the importance of platelets in tumor metastasis, rheumatoid arthritis, and severe sepsis. Some anti-platelet therapies exist for inhibiting clot formation but whether these therapies will improve clinical outcomes in these other diseases is unknown. An opportunity for significant advancements in the management and treatment for a variety of diseases focuses on further defining the “Power of the Platelet”.



## Poster #6

### **Scaffolding of Potassium Channels in Cerebral Arteries and its Potential Implication for Stroke during Beta-Blocker Therapy**

Christopher L. Moore, Bhavya B. Chandrika, Piper L. Nelson, Mathew Steephan, Nancy J. Rusch, Sung W. Rhee

More than seventy million Americans are afflicted by high blood pressure, which is the leading risk factor for stroke. Proteins called potassium channels in the muscle cells of cerebral arteries regulate blood flow to the brain. Our project investigates a novel scaffolding molecule (PSD95) in the muscle cells of small cerebral arteries that may ensure the location and function of potassium channels to optimize blood flow to the brain. Of interest, PSD95 plays a key role in keeping cerebral arteries open and may help lower the risk of stroke in patients on beta-adrenergic receptor blockers (“beta blockers”), a class of drugs used widely to treat heart conditions and high blood pressure. We utilize rat models of hypertension and apply a wide range of techniques that include imaging the diameter responses of isolated and in-situ cerebral arteries, gene knockdown and disruption of protein interaction in arteries, electrophysiological studies of isolated smooth muscle cells, and super resolution microscopy. Our goal is to identify for the first time a key scaffolding protein that serves as the “glue” in cerebral arteries to closely assemble cell components required for dilating cerebral artery, so these molecules can efficiently signal to each other to optimize cerebral blood flow to the brain. We hope to minimize abnormalities of cerebral blood flow to reduce the incidence of stroke caused by drug effects and cardiovascular diseases including hypertension. *Supported by NIH R01 HL097107.*

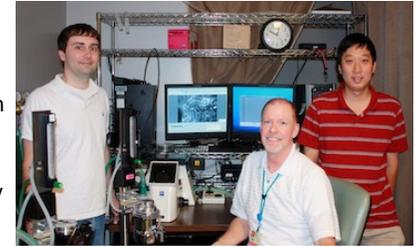


## Poster #7

### **Identification and Preclinical Evaluation of New Therapeutic Targets to Treat Sepsis-Induced Kidney Injury**

Joseph H. Holthoff, When Wang, Naeem K. Patil, Philip R. Mayeux

Sepsis is caused by a systemic microbial infection and is the major cause of death among critically ill patients, especially the elderly. Development of kidney failure is common during severe sepsis and more than doubles the mortality rate to near 75%. Unfortunately, the treatment for septic patients remains nonspecific supportive care. Using intravital videomicroscopy in a clinically relevant rodent model of polymicrobial sepsis we have shown that kidney dysfunction develops rapidly during sepsis and is correlated with kidney macro- and microcirculatory failure that leads to key pathological insults including regional hypoxia, the generation of oxygen radicals, an damage to kidney cells. Results from our detailed time course studies revealed several potential new therapeutic targets, which might halt injury and allow recover of renal function. To test this hypothesis we evaluated the therapeutic potential of agents targeting these pathological events using a clinically relevant delayed dosing paradigm to mimic therapy in humans. Our findings suggest that it may be possible to targets specific events during sepsis in humans that allow the kidney to recover and improve survival.



## Poster #8

### **Successful Microbubble Sonothrombolysis Without Tissue Plasminogen Activator in a Rabbit Model of Acute Ischemic Stroke**

William C. Culp, John D. Lowery, Aliza T. Brown, Leah J. Hennings, Paula K. Roberson, Jeff H. Hatton, Sean D. Woods, Rene Flores, Michael J. Borrelli

**Background:** Microbubbles (MB) combined with ultrasound (US) have been shown to lyse clots without tissue plasminogen activator (tPA) both *in vitro* and *in vivo*. We compared three types of MB lysis in a rabbit stroke model.

**Methods:** All rabbits (n=74) received internal carotid angiographic embolization of clots (0.6x4.0 mm) causing strokes. Groups included: 1) control (n=11), 2) tPA (n=20), 3) tPA+US (n=10), 4) Perflutren Lipid MB+US (n=16), 5) albumin 3 $\mu$ m MB+US (n=8), and 6) tagged albumin 3 $\mu$ m MB+US (n=9). Treatment began 1 hour following embolization. Ultrasound was given for 1 hour and rabbits with tPA got standard IV tPA over 1 hour. Lipid MB, 3 $\mu$ m MB, or 3 $\mu$ m MB tagged with eptifibatide and fibrin antibody dose was IV (0.16 mg/kg) over 30 minutes. Rabbits were euthanized at 24 hours. Infarct volume was determined. Hemorrhage was evaluated on H&E sections.

**Results:** Infarct size was much smaller for rabbits treated with Lipid MB+US (1.0% $\pm$ 0.6%; P=0.013), 3 $\mu$ m MB+US (0.7% $\pm$ 0.9%; P=0.018), and tagged 3 $\mu$ m MB+US (0.8% $\pm$ 0.8%; P=0.019) compared with controls (3.5% $\pm$ 0.8%). The three MB types collectively had smaller strokes (P=0.0043) than controls or all tPA (P=0.02). Infarct volume averaged 2.2% $\pm$ 0.6% and 1.7% $\pm$ 0.8% for rabbits treated with tPA alone and tPA+US, respectively.

**Conclusions:** These MB are effective in decreasing stroke size and may reduce bleeding in stroke patients. Study of human stroke application and further MB development are urgently needed.

