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PROGRAM AND ABSTRACTS

**Association of University Cardiologists
Forty-Ninth Annual Meeting
Renaissance Vinoy Resort
St. Petersburg, Florida**

January 6 – 8, 2010

2010

2010 AUC ANNUAL MEETING
PROGRAM

Wednesday, January 6, 2010

2:00 PM – 5:00 PM Council Meeting – Dann
3:00 PM – 5:00 PM Emeritus Forum – Plaza AB
6:00 PM – 8:00 PM **Reception** – Mezzanine Terrace

Thursday, January 7, 2010

7:45 AM – 8:45 AM Continental Breakfast – Royal Foyer
8:45 AM – 12:00 PM **The President's Program - Royal Ballroom**
8:45 – 9:45 **THE 24th GEORGE BURCH MEMORIAL LECTURE**

MicroRNA Control of Cardiovascular Development & Disease
Eric N. Olson, Ph.D., UT Southwestern Medical Center at Dallas

9:45 – 10:30 **FEATURED LECTURE**
A Cardiologist Confronts Obesity
Allyn Mark, M.D., University of Iowa

10:30 – 11:00 Break – Royal Foyer

11:00 – 11:45 **PRESIDENT'S LECTURE**
Muscle Ischemia in Muscular Dystrophy: Translational Research from Mice to Men
Ronald G. Victor, M.D., Heart Institute, Cedars-Sinai Medical Center

11:45 – 12:00 Discussion

12:00 – 1:00 Lunch – Majestic Ballroom

1:00 – 5:10 **First Scientific Session – Royal Ballroom**

1:00 – 1:05 Introduction of New Members in Attendance:

Craig Basson	Peter Ganz
Steven Bailey	Dan Roden
C. Noel Bairey-Merz	Lawrence Young
Anne Curtis	



2010 AUC ANNUAL MEETING
PROGRAM

Thursday, January 7, 2010, cont.

1:05 – 1:35 *Pleiotropine (PTN) Reprograms Macrophages into functional Endothelial Cells and is Expressed in Vascularized Human Atherosclerotic Plaques: IFN- γ /JAK/STAT1 Signaling is Critical for the Expression of PTN in Macrophages*
P. K. Shah, M.D., Director, Division of Cardiology & Atherosclerosis Research Center, Cedars-Sinai Heart Institute

1:35 – 2:05 *Statin Therapy for the Prevention of Atrial Fibrillation*
Anne B. Curtis, M.D., Professor of Medicine, Chief, Division of Cardiology, Director, Cardiovascular Services, University of South Florida

2:05 – 2:35 *Transcription Regulation of Coronary Blood Vessel Development*
Craig T. Basson, M.D., Professor, Director, Cardiovascular Research, Weill Medical College of Cornell University

2:35 – 3:05 *Molecular and Cellular Imaging Using Ultrasound Contrast Agents*
Flordeliza S. Villanueva, M.D., Associate Professor of Medicine, Director, Director, Non-Invasive Cardiovascular Imaging, Director, Center for Ultrasound Molecular Imaging & Therapeutics, University of Pittsburgh Medical Center

3:05 – 3:20 Break

3:20 – 3:50 *Sex/Gender Differences in CVD – A Model for Translation to Improved Outcomes*
C. Noel Bairey-Merz, M.D., Professor of Medicine, Medical Director, Preventive and Rehabilitative Cardiac Center, Director, Women's Heart Center, Cedars-Sinai Medical Center

3:50 – 4:20 *Role of the Epicardium in NonIschemic Ventricular Tachycardia*
David J. Wilber, M.D., Professor of Medicine, Director, Division of Cardiology & Cardiovascular Institute, Loyola University Medical Center

2010 AUC ANNUAL MEETING
PROGRAM

Thursday, January 7, 2010, cont.

4:20-4:50 *Rethinking Resynch: It More than Meets the Eye*
David A. Kass, M.D., Professor of Medicine and
Biomedical Engineering, Johns Hopkins
University School of Medicine

4:50 PM **Adjourn for the day**

7:00 PM – 11:00 PM **RECEPTION AND DINNER (BLACK TIE)**

7:00 – 8:00 Reception **Palm Court Terrace**

8:00 – 11:00 Dinner **Majestic Ballroom**

Friday, January 8, 2010

7:30 AM – 8:00 AM Continental breakfast – **Royal Foyer**

8:00 AM – 9:00 AM **Business Meeting – Royal Ballroom**

Memorial Minutes
Election of New Members
Election of Officers
Other New Business

9:00 AM – 12:00 PM **Second Scientific Session** **Royal Ballroom**

9:00 – 9:30 *Molecular Mechanisms Regulating Vascular Tone
and Blood Pressure*
Michael E. Mendelsohn, M.D., Elisa Kent
Mendelsohn Professor of Molecular Cardiology
and Medicine, Tufts University School of Medicine



2010 AUC ANNUAL MEETING
PROGRAM

9:30 – 10:00 *Dabigatran versus Warfarin in Patients
With Atrial Fibrillation*
Michael Ezekowitz, M.D., Ph.D.
Vice President, Lankenau Institute for
Medical Research, Vice President, Clinical
Research, Main Line Hospitals

10:00 – 10:30 Break

10:30 – 11:00 *Dysregulation of G-Protein Signaling and Right
Ventricular Outflow Tract Tachycardia*
Bruce B. Lerman, M.D., Chief Division of Cardiology,
Director, Cardiac Electrophysiology Laboratory, Weill
Medical College of Cornell University

11:00 – 11:30 *Intrinsic Cardiac Nerve Activities and the Spontaneous
Onset of Atrial Tachycardia*
Peng-Sheng Chen, M.D. Medtronic-Zipes Chair of
Cardiology, Director, Krannert Institute of Cardiology,
Chief, Division of Cardiology

11:30 – 12:00 *Increased Left Ventricular Mass is Associated With Long-
term Blood Pressure Variability beginning in Childhood in
Black Adults: The Bogalusa Heart Study*
Gerald S. Berenson, M.D., Emeritus Boyd Professor,
LSU Medical Center, Director, National Center for
Cardiovascular Center Tulane Center for Cardiovascular
Health

Adjourn



Pleiotrophin (PTN) reprograms macrophages into functional endothelial cells and is expressed in vascularized human atherosclerotic plaques: IFN- γ /JAK/STAT1 signaling is critical for the expression of PTN in macrophages

P.K. Shah, MD, From the Division of Cardiology, Oppenheimer Atherosclerosis Research, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Pleiotrophin (PTN) is an angiogenic factor thought to be important in the neovascularization associated with aggressive tumors and ischemic tissues. Using Suppressive Subtractive Hybridization, we have recently shown that PTN is expressed in athero-prone coronary arteries but not in athero-resistant mammary arteries. Furthermore, we have also demonstrated that PTN induces transdifferentiation of macrophages into functional endothelial cells capable of vasculogenesis using several different experimental approaches. Although angiogenesis and intraplaque hemorrhage can accelerate atherosclerosis, nothing is known about the function of PTN in atherogenesis. Immunostaining of vascularized human atherosclerotic plaques demonstrated a strong colocalization of PTN with microvessels and macrophages in the lesions. Using mouse and human macrophages and quantitative PCR analysis, we found that IFN- γ , but not LPS, M-CSF, ox-LDL or TNF- α , markedly induced PTN mRNA expression in a time- and dose-dependent manner, pointing to the specific role of T-cell and macrophage interactions in the expression of PTN. Mechanistic studies revealed that the Janus kinase inhibitors, WHI-P154 and ATA, efficiently blocked STAT1 phosphorylation in a concentration- and time-dependent manner. Importantly, the level of phosphorylated STAT1 was found to be directly correlated with the PTN mRNA levels. In addition, STAT1/STAT3/p44/42 signaling molecules were found to be phosphorylated by IFN- γ in macrophages and translocated into nucleus. Further, PTN promoter analysis showed that a gamma activated sequence located at -2086 to -2078 bp is essential for IFN- γ -regulated promoter activity. Moreover, electrophoretic mobility shift, supershift, and chromatin immunoprecipitation analyses revealed that both STAT1 and STAT3 bind to the gamma-activated sequence at the chromatin level in the IFN- γ stimulated cells. Finally, to test whether the combined effect of STAT1/STAT3/P44/p42 signaling is required for the expression of PTN in macrophages, gene knockdowns of those transcription factors were performed using si RNA. Indeed, cells lacking STAT1, but not STAT3 or P42, markedly reduced PTN mRNA level. These data highlight the role of inflammatory cells in the expression of PTN in the highly vascularized plaques. We are currently developing Apo E-/- PTN-/- double knockout mice to more clearly define the role of PTN in atherogenesis.

Statin Therapy for the Prevention of Atrial Fibrillation

Anne B. Curtis, MD, Kevin Kip, PhD, Charles Lambert, MD, PhD, Maureen Groer, PhD, RN. University of South Florida, Tampa, FL

Background: AF is the most common sustained arrhythmia in the adult population, yet currently available antiarrhythmic treatment is only modestly effective. There is strong evidence that inflammation contributes to the pathogenesis of AF. Atorvastatin is an HMG-CoA reductase inhibitor (statin), a class of drugs that has been shown to have beneficial anti-ischemic, antiarrhythmic, and anti-inflammatory effects, in addition to their lipid-lowering properties. Clinical studies of the use of statins for the treatment of AF have been limited. Therefore, we will test the hypothesis that the established anti-inflammatory actions of atorvastatin will delay the time to first recurrence of symptomatic AF in patients with objective evidence of systemic inflammation.

Methods: We have designed a prospective, randomized, placebo-controlled multicenter clinical trial of atorvastatin therapy versus placebo for the prevention of recurrences of AF. Patients eligible for the study will be in sinus rhythm at the time of enrollment and have a history of at least one episode of symptomatic AF documented within the preceding three months along with an elevated high sensitivity C-reactive protein level (≥ 2.0 mg/L). Six hundred patients will be recruited and followed for one year. The primary endpoint of the study is the time to first symptomatic recurrence of AF. An important secondary endpoint is total AF burden, as determined from full disclosure monitors in a subset of 150 patients in the study at baseline and at six months. We will also determine the effect of atorvastatin on symptomatic and asymptomatic recurrences of AF with intermittent monitoring over the 12 month followup period. As the hypothesis of the study is that inflammation is the mechanism by which atorvastatin would affect the natural history of AF, we will test the effects of atorvastatin on well-established circulating non-specific mediators of inflammation such as plasma C-reactive protein and determine whether a change in these biomarkers is associated with a delay in first recurrence of AF.

Conclusion: The significance of the research is that it would demonstrate that a novel, non-antiarrhythmic drug strategy is effective in the treatment of AF. Such an approach would have a widespread public health impact on reducing the burden of AF. In addition, mechanistic insight into the pathogenesis of AF recurrence and drug response will be provided by the biomarker studies.

Transcriptional Regulation of Coronary Blood Vessel Development

Nata Diman, PhD, Gabriel Brooks, MD, Boudewijn Kruithof, PhD, Cathy J Hatcher, PhD, Craig T Basson, MD, PhD, Center for Molecular Cardiology, Division of Cardiology, Weill Cornell Medical College, New York, NY

Anomalies of the coronary artery are associated with both human morbidity and mortality, but their genetic etiologies remain unclear. *TBX5*, a T-box transcription factor, plays a critical role in the development of the cardiovascular system. Mutations in the human *TBX5* cause the familial disorder Holt-Oram syndrome, characterized by congenital heart malformations in the setting of upper limb deformity. *Tbx5* is expressed not only in the myocardium, but also in the coronary vasculature and epicardium and the proepicardial organ. Coronary vascular endothelium and smooth muscle arise from cells that originate in the proepicardial organ, migrate over the heart to form epicardium, and then migrate into the myocardium and undergo epithelial to mesenchymal transformation. Our studies show that *Tbx5* modulates migration of proepicardial cells and coronary blood vessel development. We have used mouse genetic engineering to demonstrate that pro-epicardial loss of *Tbx5* produces a delay in epicardial formation, altered epicardial structure, and impaired myocardial vascularization. The consequence is a subclinical myocardial hypoxia that could produce an insidious progressive cardiomyopathy. We further hypothesized that *Ets2* might be a downstream mediator of *Tbx5*. We have shown that proepicardial expression of *Ets2* is *Tbx5* dependent. Inhibition or overexpression of *Tbx5* in proepicardial cells decreases or increases *Ets2* expression respectively. By *in situ* hybridization, we demonstrate that *Ets2* and *Tbx5* are co-expressed in the proepicardium in stage 14-17 chick embryos and in the epicardium at stage 20-24 chick embryos, a critical point in which their shared effects may mediate coronary vasculogenesis. Differential expression of *Ets2* and in non-proepicardially derived cardiac outflow tract suggests independent activities in other lineages. To determine the functional contributions to coronary vasculogenesis, we employed antisense technology to knockdown either *Tbx5* or *Ets2* expression. We have shown that antisense knockdown of *Tbx5* impairs proepicardial migration. We also demonstrate significant inhibition of cell migration by *Ets2* knockdown in primary proepicardial explant cultures. These findings support the hypothesis that *Ets2* acts in a common pathway with *Tbx5* to regulate proepicardial cell migration and coronary vasculogenesis. (Supported by NIH R01-HL80663, RC1-HL100579, HHMI, the Smart Cardiovascular Fund, and Beverly and Raymond Sackler.)



Molecular & Cellular Imaging Using Ultrasound Contrast Agents

Flordeliza S. Villanueva, M.D., Center for Ultrasound Molecular Imaging and Therapeutics, University of Pittsburgh Medical Center, Pittsburgh, PA

Ultrasound contrast agents used in clinical cardiology are gas-filled microspheres (microbubbles) that are 3-4 μm in diameter which have intravascular kinetics comparable to that of red blood cells. In the presence of an ultrasound field at the appropriate frequency and acoustic power, these microbubbles can be induced to oscillate (expand and contract), resulting in unique acoustic emissions that can be detected by non-linear ultrasound imaging systems. This property is the basis for the use of contrast agents as red blood cell tracers for left ventricular cavity opacification during echocardiography and for ultrasound perfusion imaging of the myocardium.

The non-linear oscillations of microbubbles in an ultrasound field are also the basis for novel applications of these contrast agents for molecular diagnostics and therapies utilizing ultrasound. The surface of the microbubbles can be modified to display targeting ligands that confer specific binding of the microbubbles to endothelial epitopes that are overexpressed in cardiovascular disease, for example. Binding of the microbubbles to the target manifests as a persistent contrast effect during non-linear ultrasound imaging. We have designed microbubbles to bind to families of leukocyte adhesion molecules via a monoclonal antibody or peptide sequences on the microbubble shell. This approach can detect inflammatory states such as cardiac transplant rejection. We have shown that targeted echocardiographic imaging of selectin molecules detects myocardial ischemic memory, which may lead to the more sensitive and specific diagnosis of cardiac chest pain in patients presenting to the emergency department with chest discomfort of uncertain etiology. Ultrasound molecular imaging of angiogenesis is also possible using vascular endothelial growth factor 121 (VEGF121) as the targeting moiety and other peptide sequences which bind specifically to angiogenic endothelium.

We have also demonstrated the potential to track the *in vivo* fate of stem cells using polymer microbubbles that are internalized by human mesenchymal stem cells, rendering the cells acoustically active. The ability to ultrasonically image the *in vivo* fate of cell therapies should facilitate the translation and optimization of cell therapies in cardiovascular disease. Finally, the unique behaviors of microbubbles in an ultrasound field are also the bases for therapeutic applications such as drug and gene delivery using ultrasound-mediated microbubble destruction. The ultimate translation of these promising applications of microbubble-ultrasound interactions will require multidisciplinary collaborations in bioengineering, chemistry, physiology, acoustics, physics, clinical medicine/imaging, and molecular biology.



Sex/Gender Differences in CVD – A Model for Translation to Improved Outcomes

C. Noel Bairey-Merz, CJ Pepine, LJ Shaw, LD Johnson, B Sharaf, V Bittner, GD Braunstein, R Azziz, E Handberg, C Shufelt, M Minissian, G Sopko, SF Kelsey, for the WISE Study Group, Cedars-Sinai Medical Center, Los Angeles, CA, University of Florida, Gainesville, FL, University of Pittsburgh, Pittsburgh, PA

The NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) has documented a high prevalence of coronary vascular dysfunction in women with symptoms and evidence of ischemia with no obstructive CAD. The condition is associated with an adverse prognosis and healthcare costs similar to obstructive CAD, there are an estimated 2-3 million women with existent disease, and a projected 100,000 new cases annually. This places the prevalence, morbidity and costs of coronary vascular dysfunction higher than all female reproductive cancers combined. Prospective testing of a noninvasive approach for diagnosis and prognosis is needed as critical next steps toward translation of our findings into clinical care. Established WISE core laboratories and clinical sites have provided new understanding and tools for estimating prognosis for adverse outcomes. The WISE studies have conducted clinical trials to test therapeutic interventions. Results have provided practicing physicians with the ability to translate the findings into clinical care for improved IHD outcomes.

1. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, Rogers WJ, Wessel TR, Arant CB, Pohost GM, Lerman A, Quyyumi AA, Sopko G. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006;47:S4-20.
2. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21-9.

ROLE OF THE EPICARDIUM IN NONISCHEMIC VENTRICULAR TACHYCARDIA

David J Wilber MD, Loyola University Medical Center

Ventricular tachycardia (VT) arises through multiple mechanisms including triggered activity, automaticity and reentry. The substrates for these processes are typically localized in the subendocardium. Recent experience with catheter ablation of these arrhythmias has indicated that endocardial approaches are often unsuccessful in eliminating VT, prompting an exploration of alternative sites of origin. The development of a percutaneous subxyphoid approach to accessing the ventricular epicardium for mapping and ablation over the past 10 years has permitted a more detailed evaluation of epicardial substrates in generating VT.

In patients without demonstrable structural heart disease, focal mechanisms of VT predominate. In ~10% of patients, endocardial sites of origin cannot be identified. In our experience with 30 such patients, 23 had a focal origin of VT arising near the coronary vasculature or cardiac valves. These VTs were catecholamine enhanced and when sustained, could not be entrained but could be terminated by adenosine; these features are most compatible with triggered activity. Ablation is feasible and frequently successful, but procedural modifications are required to avoid injury to adjacent structures. In remaining patients, VT arose remote from valvular or vascular structures, with activation patterns suggesting simultaneous breakthrough on both endocardium and epicardium. A potential intramural source of focal activity is suggested by successful ablation of overlying endocardial and epicardial surfaces.

In patients with nonischemic dilated cardiomyopathy (NIDCM), VT is commonly due to macroreentry involving circuits incorporating surviving muscle fibers embedded with regions of scar and fibrosis, similar to post infarction VT. Recent studies in our laboratory and others demonstrate key differences in the substrate between patients with NIDCM compared to post MI VT. NIDCM is associated with a larger area of epicardial relative to endocardial scar, and a greater frequency of epicardial diastolic potentials (indicative of delayed activation of surviving muscle bundles). In a series of 60 patients with NIDCM undergoing ablation, at least one VT required mapping and ablation in the epicardial space in 50% of patients. While these latter VT circuits were most commonly confined to the epicardial surface, combined epicardial and endocardial ablation of an intramural component was required in several patients. VT in patients with right ventricular cardiomyopathy/dysplasia (ARVC/D) is typically due to macroreentry arising from right ventricular scar. Endocardial ablation has been frequently ineffective in achieving long-term elimination of VT. While the right ventricular wall is generally assumed to be thin, regional hypertrophy and dense scar may be responsible for the inability to produce transmural lesions. Similar to the findings in NIDCM, epicardial scar in ARVC/D is common, and often has a distribution distinctly different and of greater extent than endocardial scar. In a series of 24 patients with ARVC/D, at least one VT was epicardial in 30% of patients. The epicardium plays an important role in the generation of VT both in patients with and structural heart disease; an epicardial approach is often required for ablation.

Rethinking Resynch: It More than Meets the Eye

David A. Kass, Khalid Chakir, Takeshi Alba, Andreas Barth, Giulio Agnotti, Albert Lardo, Jennifer Van Eyk, Gordon Tomaselli, Johns Hopkins Medical Institutions, Baltimore, MD

In the late 1980's pioneers working mostly in Europe started exploring the potential to improve failing heart function by pacing it. First, the focus was on altering the PR interval to optimize filling, but this provided little change in the majority of patients. The switch was then made to pacing several places at once, particularly in hearts where conduction delay existed, and this ultimately proved far more successful. The field evolved rapidly and almost entirely at the clinical level, with cath-lab studies revealing mechano-energetic improvements, imaging studies showing restoration of mechanical "synchrony", the term cardiac resynchronization therapy (CRT) invented, multi-center clinical trials conducted, and a new therapy approved (based on a modest size study with no mortality end-point) all within a remarkably short period of 4-5 years. This speed was certainly helped by our notion that we understood the "mechanism" – i.e. that the heart with dysynchrony performs poorly and less efficiently, and rendering it synchronous was helpful. We learned that QRS duration did not optimally predict responders, and spent the next several years working on imaging methods to detect dysynchrony more accurately to target treatment. We are not yet successful in this, but more importantly, are starting to learn that the "mechanism" of CRT is far more complex and intriguing than initially thought. Wall motion may not be the sole marker for diagnosing the right patient. Only in the past few years have we developed animal models to study CRT, and are observing profound changes in underlying myocardial biology. This includes restoration of myocyte rest and β -adrenergic responsiveness by novel mechanisms, enhanced myofilament Ca^{2+} sensitivity, improved repolarizing ion currents, reversal of profound transcriptome heterogeneity, major changes in the mitochondrial proteome with increased efficiency of ATP generation; most all observed globally in the in the resynchronized heart. It's time to rethink resynch.



Molecular Mechanisms Regulating Vascular Tone and Blood Pressure

Michael E. Mendelsohn, M.D.

Hypertension, a major cardiovascular risk factor and cause of mortality worldwide, is thought to arise exclusively from primary renal abnormalities. However, the etiology of most cases of hypertension remains unexplained. Over the past decade we have been exploring the hypothesis that primary abnormalities in critical vascular tone smooth muscle cell (VSMC) proteins that regulate vascular tone can lead to abnormalities of blood pressure regulation, including hypertension. VSMC tone is regulated by Ca^{2+} -dependent and Ca^{2+} -independent contractile pathways, and vascular relaxation is regulated especially by the nitric oxide-cyclic GMP-cGMP-dependent protein kinase type I (PKG1) pathway. Over the past fifteen years, our laboratory has explored the molecular targets of PKG1 and the domains of PKG1 involved in mediating interactions with these targets. This work has defined a family of PKG1-interacting proteins involved in molecular regulation of VSMC relaxation. In this presentation we describe mice that created a selective mutation in the N-terminal protein interaction (leucine zipper) domain of PKG1 α , which disrupts the PKG1 interaction with myosin phosphatase, a critical mediator of VSMC relaxation. These mice display inherited VSMC abnormalities of contraction, abnormal relaxation of large and resistance blood vessels, and increased systemic blood pressure. Renal function studies and responses to changes in dietary sodium in these PKG1 α mutant mice are normal. These data reveal that PKG1 α is required for normal VSMC physiology and support the idea that high blood pressure can arise from a primary abnormality of vascular smooth muscle cell contractile regulation, suggesting a new approach to the diagnosis and therapy of hypertension and cardiovascular diseases.



Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Michael Ezekowitz, M.D., Ph.D.

Background: Warfarin is very effective in reducing stroke in patients with atrial fibrillation but is difficult to use. Dabigatran is a new “user friendly” oral direct thrombin inhibitor.

Methods: In a non-inferiority trial, 18,113 patients with atrial fibrillation at risk of stroke were randomized to blinded fixed doses of Dabigatran 110 mg or 150 mg twice daily versus unblinded adjusted warfarin. Median follow-up was 2.0 years. The primary outcome was stroke or systemic embolism.

Results: Rates of the primary outcome were 1.69% per year on warfarin versus 1.53% per year on Dabigatran 110 mg (relative risk 0.91, 95% confidence interval 0.74 to 1.11; p [non-inferiority] <0.001) and 1.11% per year on Dabigatran 150 mg (relative risk 0.66, 95% confidence interval 0.53 to 0.82; p [superiority] <0.001). Rates of major hemorrhage were 3.36% per year on warfarin versus 2.67% per year on Dabigatran 110 mg (p=0.002) and 3.11% per year on Dabigatran 150 mg (p=0.32). Rates of hemorrhagic stroke were 0.38% per year on warfarin versus 0.12% per year on Dabigatran 110 mg (p<0.001) and 0.10% per year on Dabigatran 150 mg (p<0.001). Mortality rates were 4.13% per year on warfarin versus 3.75% per year on Dabigatran 110 mg (p=0.13) and 3.64% per year on Dabigatran 150 mg (p=0.051).

Conclusions: In patients with atrial fibrillation, Dabigatran 110 mg was associated with similar rates of stroke and systemic embolism to warfarin, and lower rates of major hemorrhage. Dabigatran 150 mg was associated with lower rates of stroke and systemic embolism than warfarin, and similar rates of major hemorrhage. Both doses of Dabigatran substantially reduced intra-cerebral bleeding.

Dysregulation of G-Protein Signaling and Right Ventricular Outflow Tract Tachycardia

Bruce B Lerman, M.D. Weill Medical College of Cornell University

The most common form of “idiopathic” ventricular tachycardia is focal in origin, localizes to the right ventricular outflow tract (RVOT), is sensitive to perturbations that lower intracellular calcium, and is thought to result from cyclic AMP-mediated triggered activity due to intracellular calcium overload and delayed after depolarizations. We have previously identified a somatic mutation in the GTP binding domain of the inhibitory G protein $G_{\alpha_{i2}}$ (F200L) in RVOT tachycardia. We hypothesized that mutations in the stimulatory G protein G_{α_s} could be responsible for some forms of RVOT tachycardia, as well as other proteins involved in regulation of intracellular calcium. To that end, genomic DNA was prepared from myocardial biopsy samples obtained from 15 patients with RVOT tachycardia. Samples were obtained from the site of origin of VT and remote sites. Coding exons of G_{α_s} , $G_{\alpha_{i2}}$, A1 adenosine receptor, β -adrenergic receptor and RyR2 were PCR-amplified and subjected to automated sequence analysis. Two somatic point mutations were identified from the arrhythmogenic focus in 2 different patients, one in the adenosine receptor (A1AR R296C) and the other in G_{α_s} (W234R). In the latter case, the mutation was located in the GTP binding domain of G_{α_s} . This region is highly conserved. Stable transfection of wild-type and mutant G_{α_s} into G_{α_s} -deficient cyc⁻S49 cells revealed that this mutation elevated basal intracellular cyclic AMP levels 16 times that of wild-type G_{α_s} , consistent with a constitutively activating mutation. Guanine nucleotide binding and hydrolysis analysis showed that the mutation is characterized by loss of GTPase activity. No mutations were detected in G_{α_s} sequences from myocardial tissue sampled from regions remote from the site of origin of tachycardia. These findings suggest that somatic cell mutations in the G protein signal transduction pathway may be responsible for some forms of RVOT tachycardia.

Intrinsic Cardiac Nerve Activities and the Spontaneous Onset of Atrial Tachyarrhythmia

Eue-Keun Choi, Seong-Wook Han, Dae-Hyeok Kim, Samuel Hwang, Sameh Sayfo, Mark J. Shen, Gianfranco Piccirillo, Chun Hwang, Shien-Fong Lin, Peng-Sheng Chen, Krannert Institute of Cardiology and the Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

OBJECTIVES: Intrinsic cardiac ganglionated plexi are known to play important roles in cardiac arrhythmogenesis. We sought to directly record the intrinsic cardiac nerve activity (ICNA) and extrinsic cardiac nerve activity (ECNA) simultaneously and to test the hypothesis that ICNA always precedes the onset of spontaneous atrial tachyarrhythmia.

METHODS: We implanted Data Sciences International (DSI) radiotransmitters in 6 dogs to record ECNA (stellate ganglion nerve activity, SGNA; vagal nerve activity, VNA) and ICNA (superior left ganglionated plexi nerve activity, SLGPNA; ligament of Marshall nerve activity, LOMNA). After baseline recording, we performed intermittent rapid (640 bpm) left atrial pacing for 6 days, followed by DSI recording for one day (off pacing). This protocol repeated itself until persistent (> 48 hrs) atrial fibrillation (AF) occurred. The nerve discharges were quantified by integrated nerve activity (Int-NA).

RESULTS: Five out of 6 dogs developed persistent AF after 39 ± 24 days pacing (range 20 to 72 days). We analyzed 29 episodes of paroxysmal atrial fibrillation (PAF) and 164 episodes of paroxysmal atrial tachycardia (PAT). The PAT and PAF episodes were invariably (100%) preceded (<5 s) by ICNA. Most of PAT events (89%) were preceded by ICNA and sympathovagal co-activation, whereas 11% was preceded by ICNA and SGNA-only activation. Most of PAF events were preceded only by ICNA (72%); the remaining 28% by ECNA and ICNA together. Int-NA (in mV) from all channels was significantly increased after rapid pacing as compared to baseline (SGNA from 2.3 ± 1.3 to 2.6 ± 1.3 mV-sec, $p=0.022$; VNA from 0.7 ± 0.3 to 0.8 ± 0.2 mV-sec, $p=0.001$; SLGP from 0.7 ± 0.4 to 2.2 ± 2.0 mV-sec, $p<0.001$; LOMNA from 3.8 ± 2.5 to 5.9 ± 1.0 mV-sec, $p<0.001$). ICNA increased faster than ECNA (SLGPNA and LOMNA doubled the amplitude within 1~2 weeks while SGNA and VNA within 3 ~ 4 weeks after pacing).

CONCLUSION: Intermittent atrial pacing caused significant electrical remodeling, as evidenced by large increases of ICNA and ECNA. All PAT and PAF episodes were invariably preceded by ICNA, documenting the importance of ICNA in atrial arrhythmogenesis.



Increased Left Ventricular Mass is Associated with Long-term Blood Pressure Variability Beginning in Childhood in Black Adults: The Bogalusa Heart Study

Wei Chen, Sathanur R. Srinivasan, Litao Ruan, Gerald S. Berenson, Tulane Center for Cardiovascular Health, Tulane University, New Orleans, LA

Background: Blood pressure (BP) is a very labile physiologic parameter in health and disease. Increased 24-hour ambulatory BP variability is associated with severity of end-organ damage and a higher rate of cardiovascular events, even after adjusting for levels. This study assessed the hypothesis that long-term BP variability from childhood to adulthood, besides levels is predictive of adulthood left ventricular mass (LVM).

Methods: The longitudinal study cohort consisted of 1053 subjects (718 whites and 335 blacks; 42% males, ages = 24-48 years; mean age = 38.4 years) enrolled in the Bogalusa Heart Study. Study subjects were examined serially 4-14 times for BP from childhood to adulthood over an average of 19.7 years follow-up, since 1973, with 8515 observations of BP. Echocardiography was performed in adulthood between 2001 and 2009. The BP variability from childhood to adulthood was measured as long-term variability from mean levels.

Results: Blacks versus whites showed significantly greater BP variability (mmHg) (9.1 vs 6.7 for systolic BP, $p<0.001$ and 8.0 vs 6.6 for diastolic BP, $p<0.001$ and higher LVM index (gram/height in $m^{2.7}$) (38.8 vs 35.4, $p<0.001$). In multivariable regression analyses, adjusting for age, sex, body mass index, LDL cholesterol, glucose, and the average long-term BP levels, LVM index ($g/m^{2.7}$) in adulthood was significantly associated with systolic BP variability (mmHg) (regression coefficient $\beta=0.66$, $p<0.001$) and diastolic BP variability (mmHg) ($\beta=0.81$, $p<0.001$) in blacks, but not in whites. Importantly, the standardized regression coefficients of the BP variability were greater than those of long-term BP levels ($\beta=0.23$ vs $\beta=0.11$ for systolic BP; $\beta=0.06$ for diastolic BP).

Conclusions: These findings indicate that long-term BP variations reflecting stimulus-response characteristics are predictive of left ventricular hypertrophy in adulthood, independent of BP levels, among black individuals. These observations have implications for preventive cardiology.

Key words: blood pressure variability; left ventricular mass; Hypertension; childhood; black-white



UPCOMING MEETINGS

- January 6-7, 2011 (50th Year Anniversary of AUC)
[Arizona Biltmore, Phoenix, Arizona](#)
- January 12-13, 2012
[Carmel Valley Ranch, Carmel, California](#)

