PROGRAM

AND

ABSTRACTS

Association of University Cardiologists
Sixtieth Annual Meeting
Virtual Meeting

January 14, 2021

2021

Thursday, January 14, 2021

Pacific Standard Time (PST)	
8:00 - 8:10 AM	**President's Welcome**
8:10 – 8:40 AM	**Nanette K. Wenger Honorary Lecture** *Title: Looking in the Mirror: Striving for Racial Equity in Academic Medicine* **Speakers:** **Valerie Montgomery Rice, MD** President & Dean, Morehouse School of Medicine **Claire Pomeroy, MD** President, Lasker Foundation
8:40 AM – 8:55 AM	Discussion
9:00 AM – 9:30 AM	**The 31st GEORGE BURCH MEMORIAL LECTURE** *Title: Why are we losing the battle with heart disease in the U.S.?* **Speaker: Robert Califf, MD** Head of Clinical Policy and Strategy for Verily and Google Health Adjunct Professor, Duke University and Stanford University
9:30 AM – 9:45 AM	Discussion
9:50 AM – 10:05 AM	**BREAK**

Scientific Session:

10:05 AM – 3:10 PM	**Scientific Session**
10:05 AM – 10:10 AM	Introduction of New Members in Attendance

Sana Al-Khatib, MD	Abhinav Diwan, MD
William Fearon, MD	Samir Kapadia, MD
Rachel Lampert, MD	Eldrin Lewis, MD
Kenneth Margulies, MD	Joseph Rogers, MD
Michael Widlansky, MD	

10:10 AM – 10:25 AM	*Assessing Coronary Physiology in the Cardiac Catheterization Laboratory*

	William F. Fearon, MD, Professor of Medicine, Stanford University School of Medicine
10:25 AM – 10:35 AM	Discussion
10:35 AM – 10:50 AM	*Management of Advanced Heart Failure with Mechanically Assisted Circulation*
	Joseph Rogers, MD, Professor of Medicine, Duke University Health System
10:50 AM – 11:00 AM	Discussion
11:00 AM – 11:15 AM	**Break**
11:15 AM – 11:30 AM	*L. Plantarum 299v and Vascular Health in Humans with Coronary Artery Disease*
	Michael E. Widlansky, MD, Professor of Medicine, Medical College of Wisconsin
11:30 AM – 11:40 AM	Discussion
11:40 AM – 11:55 AM	*A Novel Mitophagy Pathway in Cardiac Myocytes Suppresses Myocardial Inflammation and Protein Aggregation*
	Abhinav Diwan, MD, Professor of Medicine, Washington University School of Medicine
11:55 AM – 12:05 PM	Discussion
12:05 PM – 12:20 PM	**Break**
12:20 PM – 12:35 PM	*Research Interests*
	Samir Kapadia, MD, Professor of Medicine, Cleveland Clinic
12:35 PM – 12:45 PM	Discussion
12:45 PM – 1:00 PM	*Preventing Sudden Cardiac Death: From Concept to Policy to Implementation*
	Sana Al-Khatib, MD, Professor of Medicine, Duke University
1:00 PM – 1:10 PM	Discussion
1:10 PM – 1:25 PM	**Break**
1:25 PM – 1:55 PM	**Business Meeting**
	Memorials
	Election of New Members

	Election of Officers
	Budget
1:55 PM – 2:10 PM	*Quality of Life in Clinical Practice: Meaningful Outcome in Heart Failure Patients* **Eldrin Lewis, MD,** Professor of Medicine, Stanford University
2:10 PM – 2:20 PM	Discussion
2:20 PM – 2:35 PM	*Psychological stress and sudden death* **Rachel Lampert, MD,** Professor of Medicine, Yale School of Medicine
2:35 PM – 2:45 PM	Discussion
2:45 PM – 3:00 PM	*Dynamic Regulation of Cardiomyocyte Mechanics by Microtubules* **Kenneth Margulies, MD,** Professor of Medicine, University of Pennsylvania
3:00 PM – 3:10 PM	Discussion
3:10 PM	**Meeting Adjourns**

Nanette K. Wenger Honorary Lecture:

Looking in the Mirror: Striving for Racial Equity in Academic Medicine

Valerie Montgomery Rice, MD, FACOG
President and Dean,
Morehouse School of Medicine

Dr. Montgomery Rice is the sixth president of Morehouse School of Medicine and the first woman to lead the free-standing medical institution. In addition to president, she also retains the deanship. A renowned infertility specialist and researcher, she is the founder and former director of the Center for Women's Health Research at Meharry Medical College in Nashville, Tenn., one of the nation's first research centers devoted to studying diseases that disproportionately impact women of color. Her dedication to leading the creation and advancement of health equity is manifested in every aspect of her work, which has led to membership in numerous organizations and boards and countless awards, such as membership in the National Academies of Science and the Horatio Alger Association. Dr. Montgomery Rice holds a bachelor's degree in chemistry from the Georgia Institute of Technology and a medical degree from Harvard Medical School. She completed her residency in obstetrics and gynecology at Emory University School of Medicine and her fellowship in reproductive endocrinology and infertility at Hutzel Hospital in Detroit, Mich. She holds an honorary degree from both the University of Massachusetts Medical School and Rush University.

Claire Pomeroy, MD, MBA
President, Lasker Foundation

Claire Pomeroy is president and CEO of the Albert and Mary Lasker Foundation which is dedicated to accelerating support for medical research. She currently serves on the Board of Trustees for the Morehouse School of Medicine and the Board of Directors for Science Philanthropy Alliance; Foundation for Biomedical Research; iBiology, Inc.; New York Academy of Medicine; and the Center for Women in Academic Medicine and Science. She also serves on the Board of Directors for Sierra Health Foundation, Haemonetics Corporation, and Becton Dickinson & Company, positions for which she receives compensation. Dr. Pomeroy was inducted into the National Academy of Medicine in 2011.

Dr. Pomeroy received her medical degree from the University of Michigan and completed her residency and fellowship at the University of Minnesota. She earned an MBA from the University of Kentucky. She received an honorary Doctor of Science degree from University of Massachusetts Medical School in 2016. Previous positions include chief of infectious diseases and associate dean for research at the University of Kentucky. She was vice chancellor and dean of the University of California, Davis School of Medicine from 2005 - 2013. She became president of the Lasker Foundation in June 2013.

Association of AUC University Cardiologists

The 31st GEORGE BURCH MEMORIAL LECTURE:
Why are we losing the battle with heart disease in the U.S.?

Robert M. Califf, MD, MACC
Head of Clinical Policy and Strategy for Verily and Google Health
Adjunct Professor, Duke University and Stanford University

Robert M. Califf, MD, MACC, is the Head of Clinical Policy and Strategy for Verily and Google Health for Verily and Google Health. Prior to this Dr. Califf was the vice chancellor for health data science for the Duke University School of Medicine; director of Duke Forge, Duke's center for health data science; and the Donald F. Fortin, MD, Professor of Cardiology. He served as Deputy Commissioner for Medical Products and Tobacco in the U.S. Food and Drug Administration (FDA) from 2015-2016, and as Commissioner of Food and Drugs from 2016-2017. A nationally and internationally recognized leader in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf is a graduate of Duke University School of Medicine. Dr. Califf was the founding director of the Duke Clinical Research Institute and is one of the most frequently cited authors in biomedical science.

Assessing Coronary Physiology in the Cardiac Catheterization Laboratory

William F. Fearon, M.D., Stanford University

Although invasive coronary angiography continues to be considered the reference standard for identifying significant coronary artery disease, we have learned that it can be misleading. Recognition of the importance of measuring coronary pressure and flow to help guide the diagnosis and treatment of patients with chest pain presenting to the catheterization laboratory has grown over the past number of years. Indices like fractional flow reserve (FFR), the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) derived from these measurements have been shown to improve patient outcomes when measured routinely. The goal of this talk is to outline the role of assessing coronary physiology, and, in particular, measuring FFR and IMR to guide treatment decisions in patients with chest pain.

Fractional Flow Reserve:
Routine measurement of FFR to guide percutaneous coronary intervention (PCI) improves outcomes when compared with the traditional angiography-guided technique. FFR-guided PCI also results in less angina, lower rates of urgent revascularization, and fewer spontaneous myocardial infarctions when compared with medical therapy alone in patients with stable coronary artery disease. Lesions with an abnormal FFR appear to have more features of plaque vulnerability, which may explain why they have higher rates of myocardial infarction when treated with medication alone. Finally, the results of the FAME 3 trial comparing FFR-guided PCI with coronary artery bypass surgery will be presented and discussed.

Index of Microcirculatory Resistance:
Realization of the importance of microvascular dysfunction as a cause for adverse outcomes in many patients with chest pain and suspected coronary artery disease has grown over the past number of years. IMR is an index which identifies microvascular dysfunction and can be derived readily in the catheterization laboratory using a single coronary pressure/thermistor tipped guidewire. IMR has been shown to be more reproducible and less variable than CFR. Unlike CFR, which interrogates the entire coronary circulation, IMR is specific for the coronary microvasculature. In patients who have undergone successful primary PCI for ST segment elevation myocardial infarction, IMR is an independent predictor of long-term mortality, unlike other measures of microvascular function such as CFR and TIMI myocardial perfusion grade. IMR is also predictive of adverse outcomes in stable patients undergoing PCI. Finally, IMR can help diagnose microvascular angina as the cause for chest pain in patients presenting to the catheterization laboratory and found to have non-obstructive epicardial coronary artery disease.

The future of coronary physiology in the catheterization laboratory will reside in its role for testing new therapeutic strategies for addressing both acute and chronic microvascular dysfunction. There will also be a movement away from wire-based techniques to less invasive angiography-based methods for deriving FFR and IMR.

Management of Advanced Heart Failure with Mechanically Assisted Circulation

Joseph G. Rogers, MD, Duke University

Background: Despite innovation in medical and electrical therapies for heart failure with reduced ejection fraction, the morbidity and mortality outcomes for patients with the most advanced stages of the disease have changed little. Cardiac transplantation remains the “gold standard” treatment for end-stage heart failure but the shortage of suitable donor hearts has rendered transplant epidemiologically insignificant. The limited number of therapeutic options for this population has resulted in a series of clinical trials demonstrating the benefits of mechanically assisted circulation to lower mortality and improve functional capacity and quality of life.

Methods: Review of clinical trials that have shaped the body of knowledge in support of mechanically assisted circulation as relevant therapy for patients with advanced heart failure.

Results: Early clinical trials of left ventricular assist devices (LVADs) demonstrated that iterations that provided pulsatile flow using pusher-plate technology improved 12-month survival relative to optimal medical therapy in patients supported with inotropes (27% vs. 11%, $p=0.02$). In subsequent clinical trials, device evolution to miniaturized continuous flow pumps (CF-LVAD) demonstrated improved survival out to 2 years (58% vs. 27%, $p<0.001$). The most recent trial of a CF LVAD has demonstrated further incremental 2-year survival improvement to 79%. In addition to improved survival, consistent improvements in submaximal exercise performance (6 minute walk 204m vs. 372m, $p<0.05$) and quality have life have been demonstrated. The CF-LVADs have also been studied in patients with advanced heart failure not requiring inotropic support and shown to result in an improved combined end-point of mortality and improvement in 6MWD ($p=0.012$) with improved actuarial survival ($80 \pm 4\%$ vs. $63 \pm 5\%$, $p<0.001$). Adverse events are common in these patients, primarily related to hemo-incompatibility. Patients develop acquired vonWillebrand disease related to sheer stress in the device which contributes to the risk for hemorrhagic stroke and gastrointestinal bleeding.

Conclusion: The rapid evolution of mechanically assisted circulation with LVAD is arguably one of the most impactful therapies ever developed in cardiovascular medicine. While imperfect and in need of further refinement and adverse event mitigation, the therapy has been consistently shown to reduce mortality and improve quality of life and exercise performance.

L. Plantarum 299v and Vascular Health in Humans with Coronary Artery Disease

Michael E. Widlansky, Medical College of Wisconsin

Recent clinical trials demonstrate that systemic anti-inflammatory therapy reduces cardiovascular events in patients with coronary artery disease (CAD). The gut microbiota is an important regulator of systemic inflammation. We recently demonstrated Lactobacillus plantarum 299v (Lp299v) supplementation improved vascular endothelial function [as measured by brachial artery flow-mediated dilation (FMD)] in men with stable CAD. Additionally, Lp299v supplementation reduced systemic inflammation and increased circulating levels of propionic acid, a short-chain fatty acid (SCFA) produced almost exclusively but the gut microbiota. Additionally, Lp299v supplementation significantly changed the plasma metabolite profile using unbiased analyses, and plasma from patients taken following Lp299v supplementation reversed impaired endothelium-dependent vasodilation to acetylcholine of resistance arterioles from human with CAD. 16S rRNA analysis showed the Lactobacillus genus was enriched in post-probiotic stool samples without other changes. To begin investigating the mechanisms behind the favorable effects of Lp299v, we exposed peripheral blood mononuclear cells (PBMCs) of a healthy donor to plasma obtained before and after Lp299v supplementation from 19 men with stable CAD and assessed plasma-induced transcriptome changes. Transcripts were additionally analyzed to determine differentially regulated pathways and functional gene clusters in the underlying transcriptome results using Ingenuity Pathways (Qiagen) and DAVID 6.8 (NIAID/NIH). A composite inflammatory index (I.I.com) was calculated to assess systematic changes in inflammatory gene transcription. Transcriptome changes were correlated with brachial artery flow-mediated dilation (FMD) changes and gut microbiota composition changes. Daily alcohol users (n=4) had a significantly different response to Lp299v and were separated from the main analyses. Non-daily alcohol users (n=15) showed improved FMD and circulating IL-8, IL-12, and leptin. Nine hundred ninety-seven genes were significantly changed. I.I.com decreased (1.01±0.74 vs. 0.22±0.51; $P<0.0001$), indicating strong anti-inflammatory effects. Pathway analyses revealed the downregulation of IL-1β, interferon-stimulated pathways, toll-like receptor signaling, and an increase in regulator T-cell (T-reg) activity. GBP1, JAK2, and TRAIL transcriptional changes inversely correlated with FMD changes. Also, early data suggest knockdown of expression of FFAR3, a receptor for short-chain fatty acids with high affinity for propionic acid, blocks the favorable effects of post-Lp299v plasma on endothelium-dependent vasodilation in human resistance arterioles. These data provide a novel framework for understanding the favorable impact of Lp299v on human vascular health. Future studies should determine if similar favorable effects of Lp299v are seen in women with CAD and more specifically determine the circulating metabolites responsible for Lp299v's favorable effects.

A Novel Mitophagy Pathway in Cardiac Myocytes Suppresses Myocardial Inflammation and Protein Aggregation.

Abhinav Diwan, MD, Washington University School of Medicine

Background: Published studies from the Diwan laboratory implicate acquired lysosome dysfunction as a pathogenic mechanism in post-myocardial infarction ventricular remodeling and in proteotoxic cardiomyopathy. Acquired lysosome dysfunction also underlies myocardial inflammation, which is increasingly recognized as a driver of disease progression in heart failure. Damaged mitochondria release mitochondrial DNA, a potent trigger for activation of immune pathways. Mitophagy in cardiac myocytes in a lysosomal pathway to remove damaged mitochondria; whereby impaired lysosome function may trigger myocardial inflammation. In this regard, it remains unknown whether the innate immune system monitors mitochondrial damage to facilitate mitophagy as a first line of defense. We uncover a critical role for TRAF2, an innate immunity adaptor protein, in sensing mitochondrial damage in cardiac myocytes to trigger mitophagy and suppress myocardial inflammation. Our findings also point a novel role for mitophagy in removing myocardial protein aggregates, a pathologic feature common to human cardiomyopathy from diverse etiologies.

Methods and Results: We discovered that TRAF2, an innate immunity adaptor protein localizes to the mitochondria in human hearts, with dramatic upregulation in the setting of ischemic cardiomyopathy. TRAF2 is associated with mitochondria and mitochondria-associated membranes in cardiac myocytes; and its recruitment to the mitochondria is upregulated under conditions of mitochondrial damage with cardiac ischemia-reperfusion injury in mice. TRAF2 reciprocally regulates levels of TLR9 in cardiac myocytes, an endosomal pattern-recognition receptor that senses mitochondrial DNA released from damaged mitochondria to drive pro-inflammatory signaling.

To test its functional relevance, we generated and characterized mice with inducible cardiac myocyte-specific ablation of TRAF2 in the adult myocardium (iCMTRAF2 null). Concomitant loss-of-function of TLR9 was performed to understand its role downstream of impaired mitophagy.

Cardiac myocyte-specific TRAF2 null mice demonstrated cardiomyopathy with left ventricular (LV) dilation, reduced % LV fractional shortening (LV%FS), LV hypertrophy, myocardial macrophage infiltration and myocardial fibrosis. Mitochondrially-targeted mKeima transduction demonstrated impaired cardiomyocyte mitophagy with accumulation of ultrastructurally abnormal mitochondria. Concomitant germline TLR9 ablation prevented myocardial inflammation, and delayed development of cardiomyopathy despite presence of damaged mitochondria, demonstrating a pathogenic role for inflammation in the observed cardiomyopathy. AAV9-mediated restoration of wild-type TRAF2, but not TRAF2Rm rescued the cardiomyopathy and restored normal mitochondria on ultrastructural examination, pointing to an essential role for TRAF2-E3 ligase domain in facilitating mitophagy. Inducible ablation of TRAF2 also induces accumulation of protein aggregates in cardiac myocytes; which are also uniformly observed in human failing hearts from diverse etiologies.

Conclusion: Our data uncover TRAF2 as an innate immunity mediator that is critical in the first line of defense against inflammation and protein aggregation triggered by mitochondrial damage, by orchestrating basal mitophagy and suppressing pro-inflammatory TLR9 signaling in cardiac myocytes. These observations also point to a novel signaling mechanism whereby mitochondria act as a receptacle for abnormal proteins, and provide a strong rationale to stimulate mitophagy to prevent and treat heart failure.

Research Interests

Samir Kapadia, MD, Cleveland Clinic Foundation

Over the last 25 years, I have worked on several research fronts including basic research, outcome research including randomized clinical trials, device innovations, and operational research.

My basic science experience was in cell biology with Dr. Douglas Mann at the Baylor College of Medicine in Houston, Texas. We demonstrated that cardiac myocytes can produce TNFα in response to pressure overload. This TNFα mediates negative inotropic effects via P55 receptors and protective effects via p75 receptors. We also showed that TNFα and both receptors are upregulated in failing human hearts as well in patients with aortic stenosis and mitral regurgitation.

While at Cleveland Clinic, I have been involved in outcome research with focus on coronary, peripheral, and structural interventions. In coronary work, I focused on left main, multivessel interventions in stable coronary disease. I studied alcohol ablation outcomes for hypertrophic obstructive cardiomyopathy and PFO closure in initial years. In recent years, I have concentrated my efforts to percutaneous treatment of valvular heart disease. This includes steering committee membership in PARTNER and COAPT trials. I focused on procedural stroke and prevention strategies.

I have been the national PI for 4 major trials. WATCH TAVR studied watchman and TAVR as combined procedure compared to TAVR alone for patients with atrial fibrillation and aortic stenosis. Sentinel trial studied Sentinel emboli prevention device n the pivotal trial that led to approval of the device by FDA. I am now leading the PROTECTED TAVR randomized study which will investigate clinical benefit of the sentinel device in TAVR procedures. I am also Co PI for Carillon trial which is investigating effect of this indirect annuloplasty device to treat moderate or severe secondary mitral regurgitation.

I have special interest in developing new devices. I have 15 US patents. I developed a novel device to perform septal puncture. This device provides additional precision and safety compared to current devices. We tested this device in Germany and now it is under regulatory approval application Europe and US. We are currently working on another device to treat mitral regurgitation and have formed a company named Mitria. We plan first in man study in first quarter of 2021.

My current position as Chairman of Cardiovascular Medicine at Cleveland Clinic has provided me with unique opportunity develop new programs for research and innovation. I have focused on developing 2 research areas for the department including a robust cardiovascular genetics program and machine learning / artificial intelligence program. I am working on securing philanthropic funds and recruitment of talent. I am also developing collaboration with industry and other academic centers.

Overall, I am grateful of tremendous research and innovation opportunities that I have been provided at the Cleveland Clinic and I am looking forward to expanding these over coming years for our young faculty.

Preventing Sudden Cardiac Death: From Concept to Policy to Implementation

Sana M. Al-Khatib, MD, Duke University

Sudden cardiac death (SCD) is the most common mode of death in the United States affecting close to 350,000 persons every year. In my career, I have focused on identifying patient groups at an increased risk of SCD (e.g. post-myocardial infarction, heart failure with a preserved ejection fraction, end-stage renal disease, etc…). Our team has also examined utilization of therapies that are effective at preventing SCD, and the role of the implantable cardioverter defibrillator (ICD) in patients seen in routine clinical practice and in important patient subgroups not well represented in randomized clinical trials. Randomized clinical trials have shown that the ICD is a life-saving therapy in patients with systolic heart failure. Despite this strong evidence, our team has shown significant underutilization of ICDs in patients with systolic heart failure and major sex and race disparities in their use. Our team has also elucidated reasons for this underutilization and these disparities and has proposed strategies to improve utilization of ICDs and reduce disparities. One such strategy is to measure performance and provide feedback. Based on our research, this strategy appears to have worked in the American Heart Association Get With The Guidelines-Heart Failure Registry. Another important focus for our team has been on comparing the characteristics and outcomes of patients receiving an ICD in clinical trials with those in clinical practice. We showed that while patients in clinical practice are sicker than patients enrolled in randomized clinical trials of ICDs, after propensity matching and further adjustment, survival of patients who received an ICD in clinical practice was similar to that of patients who were randomized to the ICD in the clinical trials. Both had better survival than patients randomized to medical therapy only. In another study, we examined survival associated with primary prevention ICDs in patients with an ejection fraction between 30% and 35%. We found that patients with an ICD had better survival than those with no ICD. Similarly, in another study, we found that women with a primary prevention ICD had better survival than women with no ICD. The results of many studies led by our team informed the 2017 AHA/ACC/HRS Guideline for the Management of Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death that I had the pleasure to lead. The guideline had an immediate impact on policy and patient care. Based on some of the data our team had generated and recommendations in the guideline, the Centers for Medicare and Medicaid Services concluded there was enough evidence supporting continued coverage of primary prevention ICDs in eligible patients citing the guideline in many places. Moving forward our team is conducting a clinical trial to help improve the appropriate utilization of primary prevention ICDs in eligible patients using a clinical decision support tool that has already been embedded in the electronic medical record. We are also applying machine learning to help improve risk stratification of different patient groups for SCD. We are also leading a pragmatic cluster randomized clinical trial to help improve the outcomes of patients with out-of-hospital cardiac arrest.

Quality of Life in Clinical Practice: Meaningful Outcome in Heart Failure Patients

Eldrin Lewis, MD, Stanford University

Health-related quality of life (HRQL) is a key focus for the treatment of patients with chronic cardiovascular disease such as heart failure. Historically, it has not received the attention of other outcomes such as death, hospitalizations, non-fatal adverse cardiovascular conditions, and surrogate outcomes. Over the past 4 decades, there has been increased research on HRQL and better instruments have been developed that are disease-specific and validated with clear responsiveness to change and reproducibility. Implementation of HRQL assessment in large clinical trials has resulted in stronger understanding of the impact of various interventions on changes in HRQL. Statistical differences in HRQL responses are noted in pharmacologic therapies, behavior changes, surgery and less invasive procedures. Understanding of clinically meaningful changes have been noted as well.

Based upon the increased clinical trial data using HRQL, we are at a crossroads where implementing HRQL outcome measures into clinical practice is a possibility. Studies that I have conducted demonstrated that it is feasible to implement HRQL into clinical practice and is additive to the provider-based New York Heart Association functional class assessment. Using HRQL and patient-reported outcomes in clinical practice allow for screening for depression, measuring responses longitudinally, and identifying patients who may underreport their symptom burden. Decisions about ability to undergo interventions may be aided by frailty assessment. As we redesign clinical care delivery, barriers to routine HRQL use include a) the need for shorter instruments, b) integration into electronic health records, c) instrument selection for patients with comorbid conditions beyond heart failure that may influence HRQL, d) communication structure and scoring for real-time use, and e) cost of licensing for selected instruments.

Given the preferences of patients with advancing disease that may focus more on quality than quantity of life, clinicians need to increase understanding of optimal assessment of HRQL and we should develop better strategies for widespread implementation in these measures as routine component of clinical care delivery.

Psychological stress and sudden death

Rachel Lampert, MD, Yale School of Medicine

The concept of stress-induced sudden death has been recognized for centuries, but it was only following the Northridge earthquake of 1994 that this phenomena was quantified, with a four-fold increase in SCD, unrelated to physical sequelae of the earthquake, seen on that day.

We first looked more directly at the question of whether anger or other emotions can trigger ventricular arrhythmias using a diary-based case-control study of ICD patients. Anger levels were greater prior to appropriate shock than during control periods, demonstrating that anger can trigger ventricular arrhythmias. Further, anger-triggered arrhythmias were more likely to be polymorphic, PVC-initiated, and pause-dependent, characteristics associated with lethality.

In order to explore mechanisms of anger-triggering of ventricular arrhythmias, we next looked at the impact of psychological stress in the laboratory on TWA, a measure of heterogeneity of repolarization which is long-recognized to be an important factor in arrhythmogenesis. Using an anger-recall protocol, in which pts are asked to talk about a recent event which made them angry, we found that three surface measures of heterogeneity which can be determined from holter monitoring, TWA, Tamp, and Tarea, increased significantly with this stressor in the laboratory setting. We then followed the patients longitudinally. Those who had exhibited the highest elevations of TWA with anger were most likely to have an ICD-treated arrhythmia in follow-up.

Lown was the first to evaluate the possibility that mental stress could facilitate induction of ventricular arrhythmias, in 1973. Using intracardiac catheters in a dog model, he found that more PVCs could be induced, and more easily induced, in a dog stressed by being lifted in a sling conditioned to be a noxious experience than at rest. We later looked in a similar protocol at arrhythmia induction during stress in patients with ICDs who were undergoing what was at the time routine non-invasive programmed stimulation two months post-implant, and had a history of pacer-terminated VT at their post-op study. Using a standard stimulation protocol first while awake but resting, and then during an anger-recall protocol, we found that arrhythmias induced during anger were faster and more difficult to terminate during stress.

As a next piece of the puzzle, we looked at denervation using MIBG imaging. Experimental studies have defined multiple areas in which sympathetic remodeling of the heart is arrhythmogenic. In order to determine whether changes in heterogeneity of sympathetic activation might underlie the changes in heterogeneity of repol we had seen with mental stress, we performed an anger recall protocol as described previously, on five pts with ischemic CM, and 5 controls, during MIBG imaging. We found that, while hemodynamic response to stress was similar in the two groups, anger recall decreased heart-mediastianal ratio in the pts but not normals, with no change in tetrofosmin uptake, thus increasing mismatch of sympathetic activity and perfusion, which has been seen to predict SCD. Heterogeneity of uptake in the myocardium also increased with stress in the ICM pts. Whether these findings correlate with changes in repol heterogeneity, and predict arrhythmia, is a next avenue of research.

Dynamic Regulation of Cardiomyocyte Mechanics by Microtubules

Kenneth B. Margulies, MD, University of Pennsylvania

Many risk factors for heart disease, such as hypertension, directly increase mechanical stress on the heart causing pathological myocardial remodeling. This remodeling is characterized by myocardial hypertrophy, fibrosis, changes in calcium handling and cellular remodeling that ultimately stiffen the myocardium. Prior reports indicate that healthy myocardium has a Young's modulus of 10-18 kPa, and infarcted myocardium stiffens beyond 50 kPa. Increased myocardial stiffness contributes to the elevated filling pressures observed in vivo, but no current therapy targets myocardial stiffening.

We have recently been focusing on changes in the cardiomyocyte cytoskeleton, and particularly microtubules, during pathologic myocardial hypertrophy. Advances in imaging and new insights into the regulation of microtubules by post-translational modification of alpha tubulin have permitted studies defining changes in the cardiomyocyte microtubule network (MTN) in human hearts and animal models. These studies have revealed that cleavage of the C-terminal tyrosine (detyrosination) from alpha tubulin results in stabilization of the MTN, via increased binding of to desmin at the Z-line and an overall increase in MTN density. Enzymes regulating the detyrosination/tyrosination balance are a carboxypeptidase - vasohibins (VASH 1/2), and a ligase - tubulin tyrosine tyrosine ligase (TTL).

In a series of recent studies, we have shown that increased stability and density of the MTN increases cardiomyocyte viscoelasticity. Moreover, we have found significant increases in tubulin abundance and detyrosination in hearts obtained from humans with advanced dilated and hypertrophic cardiomyopathies compared with hearts from organ donors without heart failure. Moreover, pharmacological and genetic manipulations of TTL and VASH reveal that increase tubulin detyrosination observed in failing cardiomyocytes tends to restrain both contractility and relaxation dynamics. Put differently, TTL overexpression or VASH inhibition increase both cardiomyocyte contractility and rates of cardiomyocyte relaxation without altering calcium cycling.

Most recently, we have employed novel biomaterials with tunable stiffness in the range relevant to normal and diseased myocardium (10 kPa - 50 kPa) to explore how biomechanical factors regulate the cardiomyocyte cytoskeleton. When cultured on a substrate actuated to mimic the stiffness of diseased myocardium for 48 hours, normal adult rat cardiomyocytes exhibit reductions in sarcomere shortening, slowed contraction and relaxation velocities, and alterations of the calcium transient. Cardiomyocytes cultured on stiff substrates exhibited increased cell width, increased viscoelasticity and increased microtubule detyrosination. Genetic overexpression of tubulin tyrosine ligase to reduce microtubule detyrosination was sufficient to block the induction of hypertrophy and preserve myocyte contractility on the stiff condition. Together, these data suggest that clinically-relevant increases in extracellular stiffness, as might occur during pressure overload, rapidly induce changes in cardiomyocyte size and function that are dependent upon microtubule detyrosination. Our results both demonstrate the utility of our culture platform with tunable stiffness while suggesting strategies to mitigate pathological cardiac remodeling during conditions of pressure overload.

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