



**APRIL 7-8, 2021**

Baylor  
College of  
Medicine

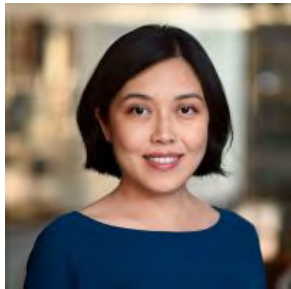
**CARDIOVASCULAR RESEARCH INSTITUTE**

**EIGHTH ANNUAL  
SYMPOSIUM  
2021**

# CVRI MISSION

The Cardiovascular Research Institute was established in 2012 to enhance collaborative opportunities for research, promote the development of new cardiovascular technologies, and to expand training programs in cardiovascular sciences.

## COURSE CHAIR



Lilei Zhang MD, PhD  
Associate Professor  
Molecular and Human Genetics  
Baylor College of Medicine

## SYMPOSIUM & SEMINAR COMMITTEE

Yuriana Aguillar, PhD	Scott Lemaire, MD
Lane Carpio	Na Li PhD
David Durgan, MD	Jing Liu, MD
Amber Eakin	Christina Magyar
Tyler Fick, MD	Ali Julian Marian, MD
Xiaoming Jia	Jack Price, MD
Mirza Umair Khalid,	Jeff Steimle, PhD
MD William Lagor, MD	Xander Wehrens, MD, PhD

## SESSION CHAIRS

David Durgan, MD  
William Lagor, MD  
Scott LeMaire, MD  
Biykem Bozkurt, MD, PhD  
Xander Wehrens, MD, PhD

# CVRI DIRECTOR

## WELCOME



Xander Wehrens, MD, PhD

Dear Colleagues,

It is with great pleasure that I welcome you to the 8th Annual Symposium of the Cardiovascular Research Institute (CVRI) at Baylor College of Medicine.

In these unprecedented times, we have faced many new challenges on a personal and global level. The COVID-19 pandemic created a halt in our everyday lives. Over the last year, we have been put great emphasis on the health and well-being of others in the community. The CVRI and Baylor College of Medicine continue to contribute and support the global effort of defeating COVID-19 and future pandemics.

The CVRI at Baylor College of Medicine was founded in 2012. One of its core missions is to promote innovative research by facilitating new collaborations across the various BCM departments and affiliated hospitals as well as throughout other institutions. The CVRI is also active in expanding training programs in cardiovascular sciences.

This year CVRI is honored to feature Dr. Alan Daugherty, Gill Foundation Chair of Preventative Cardiology and Director of the Saha Cardiovascular Research Center as the keynote lecturer. In addition, this year's symposium program features a special panel session that will focus on the impact of the SARS-CoV-2 virus on cardiovascular disease and new treatment paradigms.

On behalf of the organizing committee, I hope you will enjoy the symposium and that it provides a great opportunity to virtually meet and network with colleagues and trainees interested in cardiovascular research.

Sincerely,

Xander Wehrens, MD, PhD  
Director, Cardiovascular Research Institute  
Baylor College of Medicine

# POSTER JUDGES

Christie Ballantyne, MD  
Biykem Bozkurt, MD, PhD  
Mihail Chelu, MD, PhD  
Katarzyna Cieslik, PhD  
Thomas Cooper, MD  
David Durgan, PhD  
Mark Entman, MD  
Brian Gibson, DVM  
Ashish Kapoor, PhD  
Jason Karch, PhD  
Umair Khalid, MD  
Muge Kuyumcu–Martinez, PhD

William Lagor, PhD  
Irina Larina, PhD  
Na Li, PhD  
Shaine Morris, MD  
David Murdock, MD  
Jack Price, MD  
Anilkumar Reddy, PhD  
Vinod Vijayan, PhD  
Xander Wehrens, MD, PhD  
Huaizu Wu, PhD  
Liang Xie, PhD  
Lilei Zhang, MD, PhD

## CME INFORMATION

### Accreditation

Baylor College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

### Target Audience

Scientists, Clinicians, Physicians, Fellows, Residents, Trainees, Physician Assistants, and Nurses/Nurse Practitioners specializing in cardiovascular research and care and all others interested in cardiovascular sciences.

### Learning Objectives

- Provide a description of the heterogeneity of several facets of the aorta that may account for the regional localization of aneurysms and dissections.
- Understand the potential therapeutic value of tissue renewal in heart disease.
- Understand the basic mechanisms of cardiomyocyte proliferation and important role of cardiomyocyte regeneration in cardiac function at both physiological and pathophysiologic conditions.

## CME INFORMATION

- Introduce the latest molecular pathway associated with the pathogenesis of atrial fibrillation.
- Understand the immune response to a Chagas vaccine that results in a reduction in parasite burden in the heart and improves tissue integrity.
- Raise awareness of ongoing work to develop devices with added functionality to improve patient outcomes and appreciate ongoing efforts to develop a practical permanent heart replacement device.
- Recognize the role of a transcriptome–led approach to identify the genetic etiology of thoracic aneurysm and dissection (TAAD).
- Report on the major barriers and social determinants for developing vaccines against pandemic threats and poverty related neglected diseases.
- Understand the spectrum of acute cardiac injury in COVID–19 infection and proposed management strategies to minimize long term risk of disability.
- Understand the different mechanisms for cardiac injury in COVID–19.
- Understand the need to evaluate cardiac damage due to COVID–19 and determine the ability to return to normal activity.

### Educational Methods

Lecture, Panel Discussion, Demonstration, Question and Answer Sessions.

### Evaluation

An evaluation by questionnaire will address program content, presentation, and possible bias.

### Credit Designation

Baylor College of Medicine designates this live activity for a maximum of 6.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AVAILABLE CREDIT

- 6.25 AMA PRA Category 1 Credit™
- 6.25 Attendance



# Dr. Mark L. Entman Teaching Award for Excellence in Cardiovascular Education



Mark L. Entman, MD

William J. Osher Chair and Professor  
Cardiovascular Research  
Department of Medicine  
Cardiovascular Sciences  
Scientific Director  
The DeBakey Heart Center  
Baylor College of Medicine

Dr. Entman is Professor of Medicine, Cardiovascular Sciences, the William J. Osher Chair of Cardiovascular Research, and the Scientific Director of the DeBakey Heart Center. Dr. Entman was recruited to Baylor as an assistant professor in 1970. He was a Howard Hughes Medical Investigator from 1971–1979.

In 1977, Dr. Entman became the Chief of the Section of Cardiovascular Sciences and the Director of the Division of Research of the NHLBI National Research and Demonstration Center (now the DeBakey Heart Center) at Baylor College of Medicine and The Methodist Hospital from 1976–1985.

The Dr. Mark L. Entman Award for Excellence in Cardiovascular Education is a newly established initiative by the CVRI to recognize faculty for outstanding teaching in the graduate school curriculum.

In honor of Dr. Mark Entman's extensive contributions to cardiovascular education and research at Baylor College of Medicine, the CVRI will present this prestigious award at the annual symposium.

Dr. Entman has been an inspirational leader whose research has spanned a range of topics, including the role of myocardial calcium and sarcoplasmic reticulum function, acute inflammation and myocardial injury, and the chronic inflammatory response in cardiac repair and remodeling.

Before joining the Baylor College of Medicine faculty, Dr. Entman's training at Duke involved matriculation in the highly innovative Research Training Program designed there to promote the proper background for cellular and molecular research for MDs seeking a career in academic medicine. In 1974, his former mentor at Duke, Dr. Salih Wakil, joined the Baylor faculty as chairman of biochemistry and the two collaborated in writing the NIH training grant to establish the MD/PhD Program at Baylor, of which Dr. Entman was a co-director until 1980. In 1978, Dr. Entman became the director of the Section of Cardiovascular Sciences in the Department of Medicine and he was paramount in the new development of that program. The core curriculum for the DeBakey Heart Center Graduate Program arose from those efforts and was funded for many years by an NIH training grant which supported an independent graduate program directed by his colleague and close friend, Dr. Julius Allen. The resources of this program also provided the structure of a Basic Science Training program in Pediatric Cardiology at Texas Children's Hospital which was financed by an independent NIH training program.

Dr. Entman has given countless lectures to trainees on the Cardiovascular Sciences PhD Track and has been dedicated to furthering the educational mission at Baylor College of Medicine. Dr. Entman has mentored over 50 physician-scientists and researchers, many of whom are now leading cardiology departments and research programs across the US and world. His enthusiasm and commitment to the educational programs at Baylor College of Medicine is revered among his trainees and peers.

# KEYNOTE SPEAKER



**Alan Daugherty, PhD, DSc, FAHA**  
Associate Vice President for Research  
Director, Saha Cardiovascular Research  
Center Gill Foundation  
Chair, Preventive Cardiology  
Chair, Department of Physiology  
University of Kentucky

## SPEAKERS:



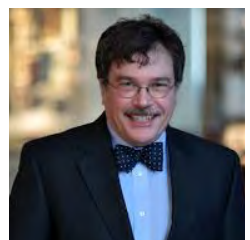
**William E. Cohn, MD**  
Vice President, Johnson & Johnson Medical  
Devices Companies (JJMDC)  
Executive Director, Johnson & Johnson  
Center for Device Innovation  
Texas Medical Center  
Professor, Department of Surgery  
Baylor College of Medicine



**Leslie T. Cooper, MD**  
Professor & Chair, Cardiovascular Medicine  
Mayo Clinic &  
Mayo Clinic Enterprise  
Jacksonville, Florida



**Nisha J. Garg, PhD**  
Professor, Microbiology & Immunology;  
Pathology Robert E. Shope, MD Distinguished  
Chair in Global Health Associate Director,  
Institute for Human Infections & Immunity  
University of Texas Medical Branch



**Peter J. Hotez, MD, PhD**  
Dean, National School of Tropical Medicine  
Professor, Pediatrics & Molecular Virology &  
Microbiology  
Baylor College of Medicine

# SPEAKERS

**Na Li, PhD**  
Assistant Professor  
Medicine, Cardiovascular Research  
Cardiovascular Research Institute  
Baylor College of Medicine



**Douglas L. Mann, MD**  
Lewin Distinguished Chair & Professor in Medicine  
Cardiovascular Disease  
Professor, Cell Biology & Physiology  
Washington University School of Medicine



**James Martin, MD, PhD**  
Professor, Molecular Physiology  
Vivian L. Smith Chair in Regenerative Medicine  
Baylor College of Medicine



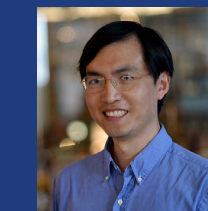
**David R. Murdock, MD, FACMG**  
Assistant Professor, Molecular & Human Genetics  
Assistant Director, Clinical Lab  
Human Genome Sequencing Center  
Baylor College of Medicine



**Sara K. Sexson Tejtzel, MD**  
Assistant Professor, Pediatric Cardiology  
Texas Children's Hospital



**Liang Xie, PhD**  
Assistant Professor  
Medicine, Atherosclerosis &  
Lipoproteins Cardiovascular Research  
Institute Baylor College of Medicine



**Peter Vanderslice, PhD**  
Director, MCRL Biology  
Molecular Cardiology Research Center  
Laboratory Texas Heart Institute



12:00 PM	<b>Welcome</b>	<b>Xander Wehrens, MD, PhD</b> Director, CVRI Professor, Molecular Biology and Physiology Juanita P. Quigley Endowed Chair in Cardiology Baylor College of Medicine
	Session I	<b>Session I Chair: William R. Lagor, PhD</b> Associate Professor, Department of Molecular Physiology and Biophysics Baylor College of Medicine
12:10 - 12:40 PM	Hippo Signaling in Heart Regeneration	<b>James Martin, MD, PhD</b> Professor Vivian L. Smith Chair in Regenerative Medicine Department of Molecular Physiology Baylor College of Medicine Director, Cardiomyocyte Renewal Lab Texas Heart Institute
12:40 - 1:00 PM	Exploring the Role of Endothelial-myocardial Interaction in Heart Regeneration	<b>Liang Xie, PhD</b> Assistant Professor Medicine, Atherosclerosis and Lipoproteins Cardiovascular Research Institute (CVRI) Baylor College of Medicine
1:00 - 1:20 PM	Molecular Mechanisms of Atrial Fibrillation New Kid on the Block	<b>Na Li, PhD</b> Assistant Professor Medicine, Cardiovascular Research Cardiovascular Research Institute (CVRI) Baylor College of Medicine
1:20 - 2:00 PM	<b>Meet the Faculty</b>	<b>Breakout Rooms</b>
2:00 - 3:00 PM	<b>Keynote Lecture</b>	<b>Session II Chair : Scott A. LeMaire, MD</b> Jimmy and Roberta Howell Professor of Cardiovascular Surgery Vice Chair for Research, Michael E. DeBakey Department of Surgery Professor of Molecular Physiology and Biophysics Director of Research, Division of Cardiothoracic Surgery Baylor College of Medicine
	<b>Aortic Heterogeneity as the Basis of Aortopathies</b>	<b>Distinguished Keynote Speaker</b>  <b>Alan Daugherty, PhD, DSc, FAHA</b> Director, Saha Cardiovascular Research Center Gill Foundation Chair, Preventive Cardiology Chair, Department of Physiology Senior Associate Dean for Research University of Kentucky
3:00 - 3:30 PM	<b>Meet the Keynote Speaker</b>	
3:30 - 4:30 PM	<b>Live Poster Review Session Judging</b>	<b>Breakout Room</b>

11:30 AM- 12:30 PM

**Welcome**

Poster Award Ceremony  
Poster Highlights

Inaugural **Mark L. Entman, MD**  
Excellence in Teaching Award

**Lilei Zhang, MD, PhD**

Assistant Professor  
Molecular and Human Genetics Baylor College  
of Medicine

**Xander Wehrens, MD, PhD**

Director, CVRI  
Juanita P. Quigley Endowed Chair in Cardiology  
Professor, Molecular Biology and Physiology  
Baylor College of Medicine

Session III

**Session III Chair: David J. Durgan, PhD**

Assistant Professor  
Anesthesiology  
Baylor College of Medicine

12:30 - 12:50 PM

Use of a Small Molecular Integrin  
Activator, 7HP349, as a Systemically  
Administered Vaccine Adjuvant in  
Controlling Chagas Cardiomyopathy

**Nisha Garg, PhD**

Professor  
Departments of Microbiology & Immunology and Pathology  
Franklin Fellow of the US Department of State - US Agency for  
International Development  
University of Texas Medical Branch

**Peter Vanderslice, PhD**

Director  
Molecular Cardiology Research Laboratory (MCRL) Biology  
Molecular Cardiology Research  
Texas Heart Institute

12:50 - 1:10 PM

The Past, Present, and Future of the  
Total Artificial Heart

**William Cohn, MD**

Vice President  
Johnson & Johnson Medical Devices Companies (JJMDC)  
Executive Director  
Johnson & Johnson Center for Device Innovation  
Texas Medical Center  
Professor, Department of Surgery  
Baylor College of Medicine

1:10 - 1:30 PM

Using RNAseq for Diagnosis and  
Gene Discovery in Thoracic Aortic  
Aneurysm and Dissection (TAAD)

**David R. Murdock, MD, FACMG**

Assistant Professor  
Molecular and Human Genetics  
Assistant Director - Clinical Lab  
Human Genome Sequencing Center  
Baylor College of Medicine

1:30- 2:00 PM

Meet the Faculty

**Breakout Room**

## Special Hot Topic Session: SARS-COV-2 AND THE HEART

### Session IV

### **Session IV Chair: Biykem Bozkurt, MD, PhD, FHFSA, FACC, FAHA, FACP**

The Mary and Gordon Cain Chair in Cardiology & Professor of Medicine  
Associate Provost of Faculty Affairs  
Senior Associate Dean of Faculty Development  
Director, Winters Center for Heart Failure Research  
Associate Director, Cardiovascular Research Institute  
Vice-Chair of Medicine  
Baylor College of Medicine  
Medicine Chief, DeBakey VA Medical Center

**2:00- 2:20 PM**

Preventing the Next Pandemic:  
Vaccine Diplomacy in a time  
of Antiscience

### **Peter Hotez, MD, PhD**

Dean, National School of Tropical Medicine  
Professor, Pediatrics, Molecular Virology and Microbiology  
Endowed Chair in Tropical Pediatrics  
Co-Director, Texas Children's Hospital Center for Vaccine Development  
Texas Children's Hospital/Baylor College of Medicine

**2:20 - 2:40 PM**

COVID-19 and Myocarditis

### **Leslie Cooper, Jr., MD**

Chair, Cardiovascular Medicine  
Mayo Clinic Enterprise  
Chair, Cardiovascular Medicine  
Mayo Clinic, Florida

**2:40 - 3:00 PM**

Myocardial Injury in COVID-19

### **Douglas L. Mann, MD**

Lewin Chair and Professor of Medicine  
Professor, Cell Biology and Physiology  
John T. Milliken Department of Internal Medicine  
Washington University School of Medicine

**3:00 - 3:20 PM**

Management of Post-COVID  
Pediatric Patients and Return to  
Activity

### **Sara Kristen Sexson Tejtzel, MD, PhD MPH**

Assistant Professor, Pediatrics  
Division of Pediatric Cardiology  
Texas Children's Hospital / Baylor College of Medicine

**3:20 - 4:00 PM**

**Meet the Faculty**

**Breakout Rooms**

**4:00 PM**

Closing Remarks

### **Xander Wehrens, MD, PhD**

Director, CVRI  
Juanita P. Quigley Endowed Chair in Cardiology  
Professor, Molecular Biology and Physiology Baylor  
College of Medicine



# KEYNOTE SPEAKER



Alan Daugherty, PhD, DSc, FAHA

Associate Vice President for Research  
Director, Saha Cardiovascular Research  
Center Gill Foundation  
Chair, Preventive Cardiology  
Chair, Department of Physiology  
*University of Kentucky*

*Alan Daugherty* was born in Liverpool, England. He completed his undergraduate studies in Pharmacology at Sunderland Polytechnic, and received both a Ph.D. and a D.Sc. from the University of Bath.

He moved to Washington University in St. Louis for fellowship training on lipoprotein metabolism and atherosclerosis. Subsequently, he was appointed to the faculty in the Division of Cardiovascular Medicine. He continued his studies on mechanisms of lipoprotein modification and immune function on the development of atherosclerosis. These studies also including imaging studies using chemical adducts for noninvasively detecting lipoprotein catabolism by a number of modalities.

In 1997, he moved to the University of Kentucky in Lexington where he is now the Senior Associate Dean for Research in the College of Medicine and Director of the Saha Cardiovascular Research Center. Through the generosity of Linda and Jack Gill, he was also awarded the Gill Foundation Chair of Preventive Cardiology. Within the strong collaborative environment for cardiovascular research at the University of Kentucky, he has participated in studies on the role of angiotensin peptides in the development of atherosclerosis and aortic aneurysms. He is highly committed to the research, advocacy, and educational missions of the American Heart Association. He is currently a charter member of the Atherosclerosis and Inflammatory Cardiovascular System NIH study section. Dr. Daugherty serves as Editor-in-Chief of Arteriosclerosis, Thrombosis, and Vascular Biology (AVTB).

<https://med.uky.edu/users/adaugh>

# FACULTY BIOGRAPHIES



William E. Cohn, MD

Vice President, Johnson & Johnson Medical Devices Companies (JJMDC) Executive Director, Johnson & Johnson Center for Device Innovation Texas Medical Center Professor, Department of Surgery Baylor College of Medicine

William E. Cohn, MD, is a Vice President at Johnson & Johnson Medical Devices Companies (JJMDC) and the Executive Director for the Johnson & Johnson Center for Device Innovation at the Texas Medical Center. He is also a professor of surgery at Baylor College of Medicine and an adjunct professor of Bioengineering at both Rice University and the University of Houston.

Prior to joining JJMDC, Dr. Cohn was the director of the Cullen Cardiovascular Research Lab at the famed Texas Heart Institute and the Director of Minimally Invasive Cardiothoracic Surgery at THI. A native of Houston, Dr. Cohn received his medical education, general surgical training, and cardiothoracic surgical training at Baylor College of Medicine where he served as the last chief resident of the legendary heart surgeon Michael E. DeBakey. After graduation, Dr. Cohn spent eleven years on the faculty of Harvard Medical School and as an Attending Cardiothoracic Surgeon at Boston's Beth Israel Deaconess Medical Center.

His major research interests include the development of new technology for decreasing the invasiveness of surgical procedures and development of the continuous-flow totally implantable artificial heart. In 2011, Dr. Cohn and Dr. O. H. Frazier successfully implanted the first pulseless total heart replacement device in a human patient.

Dr. Cohn has a passion for medical device development and has more than 90 US patents granted or pending and another 60 international patents for his medical innovations. His numerous awards include an honorary doctorate in science from Oberlin College, the Distinguished Scientist Award, given by the MacDonald Fund, and the Edison Award for excellence in human-centered design and innovation for inventing the SentreHEART® Lariat® Suture Delivery Device. In 2000, Dr. Cohn was named the distinguished Inventor of the Year by the U.S. Intellectual Property Owners Association and in 2014, he was named Outstanding Inventor of the Year by the Houston IPO. In addition, in 2014 he received an award for the most Innovative Medical Device Startup of the year at the Innovations in Cardiovascular Interventions Conference in Tel Aviv for inventing the TVA everlinQ system for percutaneous creation of AV fistulas and for founding TVA Medical. He is the Chief Medical Officer of BiVACOR Inc. and currently serves on the board of directors of CSI Inc., BiVACOR, and TVA Medical. Previously, he served on the boards of ArterX, PluroMed, Onyx Medical, and SentreHeart.

# FACULTY BIOGRAPHIES

Leslie T. Cooper, M.D., is a general cardiologist and the Chair of the Mayo Clinic Enterprise Department of Cardiovascular Medicine as well as Chair of the Department of Cardiovascular Medicine at Mayo Clinic in Florida.

Dr. Cooper's clinical interests and research focus on clinical and translational studies of rare and undiagnosed cardiomyopathies, myocarditis, and inflammatory cardiac and vascular diseases such as giant cell myocarditis, cardiac sarcoidosis, eosinophilic myocarditis, and Takayasu's arteritis.

He has published over 130

original peer-reviewed papers as well as contributing to, and editing books on myocarditis. In addition he has spent years working with clinicians and researchers around the world to further diagnosis, treatment, and care for myocarditis and cardiomyopathies. In addition to his clinical and research work Dr. Cooper is a fellow of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology Heart Failure Association, The International Society for Heart and Lung Transplantation and the Society for Vascular Medicine and Biology. He is also the founder and former president of the Myocarditis Foundation and continues to serve on their board of directors.



Leslie T. Cooper, MD

Professor & Chair  
Cardiovascular Medicine  
Mayo Clinic &  
Mayo Clinic Enterprise  
Jacksonville, Florida

# FACULTY BIOGRAPHIES



**Nisha J. Garg, PhD**

Professor, Microbiology & Immunology; Pathology  
Robert E. Shope, MD Distinguished  
Chair in Global Health  
Associate Director, Institute for  
Human Infections & Immunity  
University of Texas Medical Branch

Dr. Nisha J. Garg joined UTMB in 2000, and currently serves as the Professor in the Departments of Microbiology & Immunology and Pathology, Robert E. Shope, MD Distinguished Chair in Global Health, Associate Director of the Institute for Human Infections and Immunity. A world renowned expert in cardiomyopathy of infectious etiology, Dr. Garg serves on external review committees of NIH, American Heart Association, and other international funding agencies, editorial boards of numerous high-caliber scientific journals, including *Am J Pathol*, *American Journal of Cardiovascular Disease* and *Infection and Immunity*. She also served as Senior Scientific Advisor at the US Agency for International Development (USAID), engaged in

implementation of Neglected Tropical Diseases Initiative of the US Government in Latin America.

Dr. Garg has made substantial contributions as an investigator, educator, and mentor. She has conducted pioneering research on understanding the pathogenesis of chagasic disease of the heart that afflict millions of people, and developing unique strategies for early diagnosis and prevention of cardiac disease. In addition to her scientific achievements, Dr. Garg has an outstanding track record as a mentor, and works on initiatives to promote the careers of junior faculty in science. Dr. Garg's research program has been consistently funded by extramural sources. She has authored >120 papers in peer-reviewed journals, including the *J Am Coll Cardiol*, *Mol Cell Proteomics*, *Am J Pathol*, *Plos Pathogens*, *Internatl J Cardiol*, *MBio*, and *J Immunol*.

# FACULTY BIOGRAPHIES



**Peter J. Hotez, MD, PhD**

Dean, National School  
of Tropical Medicine  
Professor, Pediatrics & Molecular  
Virology & Microbiology  
Baylor College of Medicine

Peter J. Hotez, M.D., Ph.D. is Dean of the National School of Tropical Medicine and Professor of Pediatrics and Molecular Virology & Microbiology at Baylor College of Medicine where he is also the Co-director of the Texas Children's Center for Vaccine Development (CVD) and Texas Children's Hospital Endowed Chair of Tropical Pediatrics. He is also University Professor at Baylor University, Fellow in Disease and Poverty at the James A Baker III Institute for Public Policy, Senior Fellow at the Scowcroft Institute of International Affairs at Texas A&M University, Faculty Fellow with the Hagler Institute for Advanced Studies at Texas A&M University, and Health Policy Scholar in the Baylor Center for Medical Ethics and Health Policy.

Dr. Hotez is an internationally-recognized physician-scientist in neglected tropical diseases and vaccine development. As head of the Texas Children's CVD, he leads a team and product development partnership for developing new vaccines for hookworm infection, schistosomiasis, leishmaniasis, Chagas disease, and SARS/MERS/SARS-2 coronavirus, diseases affecting hundreds of millions of children and adults worldwide, while championing access to vaccines globally and in the United States. In 2006 at the Clinton Global Initiative he co-founded the Global Network for Neglected Tropical Diseases to provide access to essential medicines for hundreds of millions of people.

He obtained his undergraduate degree in molecular biophysics from Yale University in 1980 (phi beta kappa), followed by a Ph.D. degree in biochemistry from Rockefeller University in 1986, and an M.D. from Weil Cornell Medical College in 1987. Dr. Hotez has authored more than 500 original papers and is the author of four single-author books.



# FACULTY BIOGRAPHIES



Na Li, PhD

Assistant Professor  
Medicine, Cardiovascular  
Research  
Cardiovascular Research Institute  
Baylor College of Medicine

Dr. Li has a broad background in cardiovascular science, with specific training and expertise in cardiovascular pharmacology and electrophysiology. The research interest in Dr. Li's laboratory is to discover novel molecular mechanisms of cardiac arrhythmias. The Li lab has published a number of quintessential papers establishing the role of inflammasome signaling in the pathogenesis of atrial fibrillation. Li lab is well-funded with a number of NIH grants and a BCM CVRI pilot grant. Her lab routinely collaborates with international leading experts in the field of cardiac electrophysiology. Within Baylor, she is actively involved in teaching, participating in several didactic courses. She is the chair of the Cardiovascular Research Institute Education and Training Committee and the course director of Term 4 Advanced Topics in Cardiac Physiology and Diseases.

# FACULTY BIOGRAPHIES

Dr. Mann is the Lewin Distinguished Professor in Cardiovascular Disease and Professor of Cell Biology and Physiology. He received his medical degree from Temple University School of Medicine in Philadelphia and completed fellowships in clinical cardiology at the University of California San Diego, and Massachusetts General Hospital in Boston. He served as Chief of Cardiology at Baylor College of Medicine (2005–2009) and Washington University School of Medicine (2009–2019).

Dr. Mann's primary research interest has been the molecular and cellular basis of heart

failure, with particular emphasis on the role of innate immunity in disease progression and recovery of the failing heart. The author of numerous peer reviewed articles on the role on inflammatory mediators in cardiac remodeling and myocardial recovery, Dr. Mann is also the founding editor of Heart Failure, A Companion to Braunwald's Heart Disease, and a co-editor of Braunwald's Heart Disease, the leading textbook in cardiovascular medicine. Dr. Mann is currently the founding Editor-in-Chief for JACC: Basic to Translational Science, and is a member of the Editorial Board of Circulation, The Journal of the American College of Cardiology, and JACC Heart Failure. Among his honors are the Michael E. DeBakey award for excellence in research, the Alfred Soffer Award for Editorial Excellence, the Distinguished Mentor Award from the American College of Cardiology, the Lifetime Achievement Award from the Heart Failure Society of America. He is a member (elected) of the American Society for Clinical Investigation, the Association of American Physicians, the American Association for the Advancement in Science, the Association of University Cardiologists, and the American Clinical and Climatological Association. He is the past president of the Heart Failure Society.



Douglas L. Mann, MD

Lewin Distinguished Chair  
& Professor in Medicine  
Cardiovascular Disease  
Professor, Cell Biology & Physiology  
Washington University  
School of Medicine



# FACULTY BIOGRAPHIES



James Martin, MD, PhD

Professor, Molecular Physiology  
Vivian L. Smith Chair,  
Regenerative Medicine  
Baylor College of Medicine  
Director, Cardiomyocyte Renewal Lab  
Texas Heart Institute

Dr. Martin is an internationally recognized developmental and regenerative biologist who has made fundamental contributions to our understanding of development, disease, and regeneration. He has authored more than 140 peer-reviewed papers in top journals such as

Nature, Science, Cell, Developmental Cell, Plos Genetics, Development, and PNAS. His recent groundbreaking work on the Hippo pathway in heart size regulation is a landmark study that led to the insight that the Hippopathway is an inhibitor of adult heart muscle regeneration. Dr. Martin's insights revealed new avenues for treatment of human heart failure. Dr. Martin has made fundamental insights into the role of the transcription factor Pitx2 in atrial fibrillation, the most common sustained arrhythmia in the human population. He made use of the mouse model to investigate Pitx2 in atrial homeostasis but also in left right asymmetric morphogenesis that is essential for human development. Dr. Martin's studies investigating Pitx2 function in craniofacial development provided insight into the molecular basis of Rieger syndrome. He uncovered a pivotal function for Bmp signaling in endothelial-mesenchymal transition and cardiac valve development. Dr Martin's studies uncovered a novel role for canonical Wnt signaling in cardiac progenitor cell diversification. He found the first microRNA implicated in orofacial clefting. Dr. Martin's studies are highly cited and also reported on by the lay media.

# FACULTY BIOGRAPHIES



David R. Murdock, MD, FACMG

Assistant Professor, Molecular & Human  
Genetics Assistant Director, Clinical Lab  
Human Genome Sequencing Center  
Baylor College of Medicine

Dr. David Murdock is board-certified in internal medicine, clinical genetics, and molecular genetics, focusing on the genetics of cardiovascular disease. He is the assistant director of the Human Genome Sequencing Center CAP/CLIA-certified Clinical Laboratory (HGSC-CL) at Baylor College of Medicine (BCM), where he leads the interpretation teams for multiple efforts, including eMERGE, HeartCare, and All of Us. He also leads the sequencing interpretation team for the BCM Undiagnosed Diseases Network clinical site, where he develops analytical pipelines for exome, genome, and RNA sequencing analysis. Dr. Murdock has published extensively on genetic topics as well as sequencing technology applications in clinical practice. He is an active clinician evaluating and treating adult patients with various genetic conditions, with a particular interest in connective tissue disorders. He is a firm believer in the utility of genetic sequencing to improve health outcomes through early diagnosis, gene discovery, and understanding disease mechanisms.

[BCM.EDU/CVRI](http://BCM.EDU/CVRI) | [#BCMCVRISYMPOSIUM](https://twitter.com/BCMCVRISYMPOSIUM)

# FACULTY BIOGRAPHIES



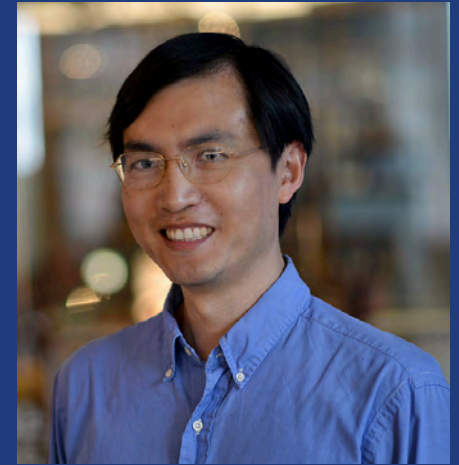
Sara K. Sexson Tejtzel, MD, PhD, MPH

Assistant Professor, Pediatrics  
Pediatric Cardiology  
Texas Children's Hospital  
Baylor College of Medicine

Dr. Sara Kristen Sexson Tejtzel is an Assistant Professor of Pediatric Cardiology at Baylor College of Medicine, Texas Children's Hospital. Her interests lie in cardiac imaging including transthoracic, transesophageal, and fetal imaging, inpatient care and continuing care of children with acquired and congenital heart disease.

Her research interests have included the use of cardiac catheterization in the post heart transplant patient, evaluation of the Kawasaki Disease guidelines, and physician adherence to guidelines. She seeks to expand my research endeavors, both at a local and a national level, to include preventive cardiology, quality improvement and outcomes of children with acquired and congenital heart disease.

# FACULTY BIOGRAPHIES



Liang Xie, PhD

Assistant Professor  
Medicine, Atherosclerosis & Lipoproteins  
Cardiovascular Research Institute  
Baylor College of Medicine

Dr. Liang Xie is an Assistant Professor in the Department of Medicine at Baylor College of Medicine. He received his PhD in Pharmacology from the University of Rochester and went on to a Post-Doctoral Fellowship in Cardiovascular Research at Duke University.

Dr. Xie studies the basic biochemistry of protein prolyl hydroxylation and its important roles of in cardiac function. His particular focuses include the understanding of the molecular mechanisms by which Prolyl Hydroxylase Domain Proteins (PHDs) regulate calcium cycling and cardiac contractile function and how their dysregulation contributes to the pathophysiological development of heart diseases such as cardiac hypertrophy and arrhythmia.



# FACULTY BIOGRAPHIES



**Peter Vanderslice, PhD**

Director, MCRL Biology  
Molecular Cardiology Research Center  
Laboratory  
Texas Heart Institute

Dr. Peter Vanderslice is the Director – Biology of the Molecular Cardiology Research Laboratory at the Texas Heart Institute in Houston, Texas. Dr Vanderslice has spent over 25 years leading teams focused on the development of small molecule compounds that bind and modulate the function of integrins, selectins, and chemokine receptors. He has authored numerous peer-reviewed publications, reviews, and book chapters focusing on the biological function and therapeutic targeting of cell adhesion molecules.

Much of his professional career has been in the pharmaceutical industry, where he gained extensive experience with each stage of the pipeline from discovery to progression into clinical trials.

As Senior Director of Drug Discovery at Encysive Pharmaceuticals, Dr. Vanderslice led teams developing therapeutics for autoimmune and inflammatory diseases. Three such programs resulted in compounds entering clinical trials. He joined the Texas Heart Institute in 2008 and has continued to discover and characterize integrin-targeted small molecules as potential therapeutics. These include a family of integrin activators that function as immune stimulants, one of which entered Phase I clinical trials in October of 2020. Dr. Vanderslice received his Ph.D. in Biochemistry from the University of Texas at Austin and trained as a Parker B. Francis postdoctoral fellow in the Cardiovascular Research Institute at the University of California, San Francisco.

# EXECUTIVE COMMITTEE



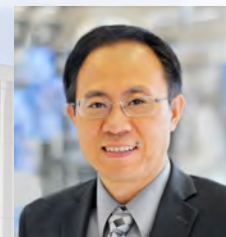
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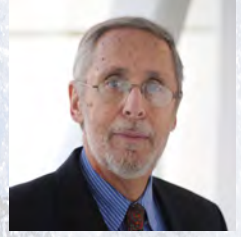
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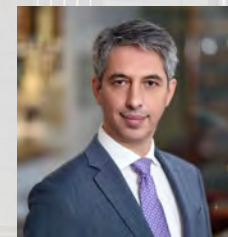
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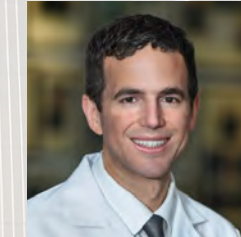
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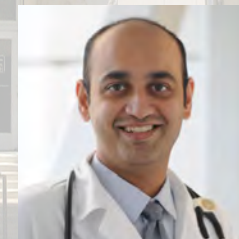
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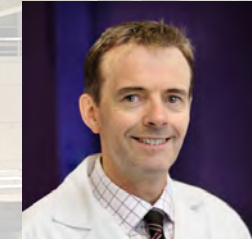
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**Daniel Penny, MD, PhD**  
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**APRIL 7-8, 2021**

**CARDIOVASCULAR RESEARCH INSTITUTE**

**ABSTRACTS**

**EIGHTH ANNUAL  
SYMPOSIUM  
2021**



## Poster Number 1

### Student

### Heart Failure

#### MYOCARDIAL REV-ERB-MEDIATED DIURNAL METABOLIC RHYTHM IN THE OBESITY PARADOX OF HEART FAILURE

Shiyang Song<sup>1</sup>, Chih-Liang Tien<sup>2</sup>, Basil Paul<sup>1</sup>, Wenbo Li<sup>1</sup>, Hui Li<sup>2</sup>, Qiying Fan<sup>3</sup>, Jong-Min Choi<sup>4</sup>, Yanfeng Xue<sup>1</sup>, Wenjun Zhou<sup>1</sup>, Andrea R. Ortiz<sup>4</sup>, Brittany Stork<sup>4</sup>, Nagireddy Putluri<sup>4</sup>, Brian York<sup>4</sup>, Sung Yun Jung<sup>4</sup>, Liang Xie<sup>3</sup>, Lilei Zhang<sup>2\*</sup>, Zheng Sun<sup>1,4\*</sup>

<sup>1</sup>Medicine-Endocrinology, Baylor College of Medicine, Houston, TX; <sup>2</sup> Molecular and Human Genetics, Baylor College of Medicine; <sup>3</sup> Medicine-Atherosclerosis and Vascular Medicine, Baylor College of Medicine; <sup>4</sup> Molecular and Cellular Biology, Baylor College of Medicine

**Background:** Nuclear receptor Rev-erb $\alpha/\beta$  are druggable components of the circadian clock. Rev-erb agonists and antagonists can benefit the heart. However, cardiac Rev-erb functions are unknown.

**Materials/Methods:** We generated a heart-specific Rev-erb knockout (Rev-HKO) mouse line using the  $\alpha$ MHC-Cre. Echocardiography and histology analysis was used to evaluate the cardiac functions, along with RNA-seq, ChIP-seq, metabolomics, lipidomics, and proteomics analysis. Isolated primary cardiomyocytes and AC16 cell line were used for metabolic flux analysis with isotope tracers.

**Results:** Rev-HKO mice display progressive dilated cardiomyopathy (DCM) and lethal heart failure by 6-8 months old. Multi-omics analyses reveal impaired fatty acid oxidation in KO myocardium preceding contractile dysfunctions, particularly in the light cycle, with a reciprocal overreliance on carbohydrate utilization, particularly in the dark cycle. Increasing dietary lipids supply in the dark cycle does not affect cardiac dysfunctions in KO mice. However, obesity coupled with systemic insulin resistance paradoxically ameliorates cardiac dysfunctions in KO mice, associated with rescued expression of lipid oxidation genes only in the light cycle in phase with increased fatty acids availability from adipose lipolysis.

**Conclusions:** These findings demonstrate a temporally coordinated interplay between clock-mediated anticipation and nutrient-induced response in myocardial metabolism, which has implications in the 'obesity paradox' of heart failure and human DCM.

## Poster Number 2

### Postdoctoral Researcher

#### Heart Failure

### AN ALTERED EXTRACELLULAR MATRIX IMPAIRS MECHANOSENSING AND FIBROBLAST-TO-MYOFIBROBLAST MATURATION IN THE AGING MALE MOUSE HEART

Aude Angelini<sup>1</sup>, JoAnn Trial<sup>1</sup>, Mark L. Entman<sup>1</sup>, Katarzyna A. Cieslik<sup>1</sup>

<sup>1</sup>Medicine-Cardiovascular Science, Baylor College of Medicine, Houston, TX

**Background:** Aging is associated with a higher risk of cardiovascular diseases. The main features of the aged heart include an altered matrix (ECM) deposition. ECM can promote the maturation of fibroblast into myofibroblast (expressing  $\alpha$ -SMA) through the mechanosensing pathway. Briefly, ECM tension usually activates the integrin signaling, which triggers actin polymerization and downstream expression of contractile  $\alpha$ -SMA. In the old male heart, fibroblasts have a reduced ability to mature into myofibroblasts. We hypothesize that this is partly due to the altered mechanosensing axis.

**Materials/Methods:** To ascertain our hypothesis, we isolated mouse fibroblasts and ECM from the heart of young (4 month-old) and old (24 month-old) male mice.

**Results:** We found that ECM deposited by old cells has an altered distribution of collagens and fibronectins, which affects the expression of Kindlin-2, a protein that bridges ECM via integrins to actin. Polymerized (F) to monomeric (G) actin ratio was also decreased by 65%. By in vitro ECM swap, both Kindlin-2 level and F/G actin ratio are 2-fold increased in old cells cultured on young matrix. In old cells, we also found increased cytosolic retention of MRTF-A, an actin-sensitive co-transcription factor (necessary for  $\alpha$ -SMA). By siRNA approach, we are now exploring how the loss of Kindlin-2 may affect mechanosensing.

**Conclusions:** In conclusion, here we found evidence that altered ECM disrupts the mechanosensing pathway and contributes to the impaired myofibroblast maturation in the aging heart.

## Poster Number 3

### Junior Faculty

### Heart Failure

#### **HIPPO PATHWAY EFFECTOR TEAD1 DRIVES TRANSDIFFERENTIATION OF CARDIAC FIBROBLASTS TOWARDS THE CARDIAC CELL LINEAGE**

Vivek P Singh<sup>1</sup>, Jaya Pratap Pinnamaneni<sup>2</sup>, Aarthi Pugazenthi<sup>2</sup>, Deepthi Sanagasetti<sup>2</sup>, Megumi Mathison<sup>2</sup>, Jianchang Yang<sup>2</sup>, James F Martin<sup>2</sup>, Todd K Rosengart<sup>2</sup>

<sup>1</sup>Surgery-Cardiothoracic, Baylor College of Medicine, Houston, TX; <sup>2</sup> Molecular Physiology and Biophysics, Baylor College of Medicine

**Background:** The efficiency of direct cell reprogramming and induction of functional cardiomyocytes remains low, especially for human cells. We therefore explored the potential of leveraging the cardio-differentiating hippo pathway to enhance the efficiency of iCM generation from fibroblasts.

**Materials/Methods:** We first screened the hippo pathway effectors YAP, TAZ, and TEAD1 (Td) for enhancing the reprogramming efficacy of the cardio-differentiating transcription factors Gata4, Mef2C, and TBX5 (GMT).

**Results:** TEAD1 (Td) replacement of TBX5 induced the greatest levels of cTnT expression compared to all other possible combinations of Td and GMT combinations (  $P < 0.001$ ). We observed that cells treated with GMTd exhibited more advanced sarcomere organization and cell contractility (beating) seen as early as 4 weeks, whereas no cells treated with GMT alone show beating. Human cardiac fibroblasts likewise demonstrated increased cTnT expression with GMTd vs GMT treatment ( $P < 0.001$ ). Reflecting a potential mechanism of action for these effects, we found that Td administration increased expression of the gene activation H3K4me4 histone mark at the promoter regions of key cardio-differentiation genes such as cTnT, Gata4 and RyR2.

**Conclusions:** These data suggest that TEAD1 is as an important regulator of cardiac reprogramming that increases the efficiency of matured iCM generation. Utilization of hippo pathway intermediates such as TEAD1 may be an important component of human cardiac cell transdifferentiation strategies.

## Poster Number 4

### Student

### Heart Failure

## THE REGULATION OF THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE BY THE ANTI-APOPTOTIC BCL-2 FAMILY MEMBERS

Pooja Patel<sup>1</sup>, Jason Karch<sup>1</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX

**Background:** Mitochondrial dysfunction is a major hallmark of necrotic cell death and is a primary cause of many cardiac pathologies. BAX/BAK play a non-canonical role in necrotic cell death, as their monomeric expression is required for MPTP-dependent mitochondrial dysfunction. The MPTP is a non-selective pore in the inner mitochondrial membrane that is activated by high levels of matrix  $\text{Ca}^{2+}$  and leads to mitochondrial dysfunction. The relationship between BAX/BAK activation and MPTP sensitization is unknown.

**Materials/Methods:** We use a combination of in vitro (cell culture) and ex vivo (isolated mitochondria) approaches to determine the role of the anti-apoptotic Bcl-2 family members in necrotic cell death and MPTP opening. To study the role of each individual family member (Mcl-1, Bcl-2, and Bclx) we utilize specific pharmacological inhibitors, referred to as BH3-mimetics. The main experimental methodologies used are flow cytometry to measure cell death and fluorometry to assess MPTP sensitivity.

**Results:** Here, we determined that all the anti-apoptotic Bcl-2 family expressed in the heart (Mcl-1, Bcl-2 and Bclx) desensitize the MPTP, increase mitochondrial  $\text{Ca}^{2+}$  capacity, and protect against dysfunction. We also determine that inhibition of each member exacerbates both apoptotic and necrotic cell death in vitro in a Bax/Bak dependent manner.

**Conclusions:** Bax/Bak inhibition by the anti-apoptotic Bcl-2 family is equally important for necrotic cell death and mitochondrial dysfunction as cytochrome-c release and apoptotic cell death.



## Poster Number 5

### Postdoctoral Researcher

#### Heart Failure

### GENETIC ENGINEERING OF ADENO-ASSOCIATED VIRUS FOR IMPROVED INFECTIVITY AND IMMUNE AVOIDANCE

Tawana M Robinson<sup>1</sup>, Michelle L Ho<sup>2</sup>, Brian Wahlig<sup>2</sup>, Maria Chen<sup>2</sup>, Michael Lam<sup>2</sup>, Veronica Gough<sup>2</sup>, Anton Banta<sup>2</sup>, Kiara Reyes Gamas<sup>2</sup>, Byungkuk Kang<sup>2</sup>, Esther Lee<sup>2</sup>, Weitong Chen<sup>3</sup>, Matt Ykema<sup>2</sup>, Junghae Suh<sup>2,3,4</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX; Bioengineering, <sup>2</sup>Rice University, Houston, TX; <sup>3</sup>Chemical and Biomolecular Engineering, Rice University

**Background:** Adeno-associated virus (AAV) is one of the most clinically utilized gene therapy vectors. Understanding the role of viral trafficking and the host immune response in therapeutic efficacy is paramount. Previous studies have shown that N-terminal regions of the AAV capsid proteins are responsible for endosomal escape and nuclear trafficking; however, the mechanisms remain unknown. Within the AAV N-terminus, we found S155 and the flanking residues; D154 and G158 (S-T mutants) are essential for AAV2 transduction efficiency. In parallel, a Nature-inspired strategy was employed to create an immune-evasive AAV vector (AAV-SP). We genetically incorporated a “self-peptide” (SP) onto the surface of the AAV2 capsid. In sum, capsid-engineering strategies may optimize AAV vectors for clinical progress.

**Materials/Methods:** With combined rational design and molecular cloning strategies, we produced AAV mutants to test for viral trafficking, transduction efficiency, and phagocytic susceptibility.

**Results:** Remarkably, specific S/T and AAV-SP capsid mutants show a range of functional importance within 5 to 10-fold decrease in viral transcription and phagocytic susceptibility, respectively.

**Conclusions:** Through genetic modification of the AAV capsid, we found several amino acid residues that are necessary for viral infectivity. Also, we generated a panel of vectors with inserted peptides in the AAV capsid to evade immune cell uptake.

## Poster Number 6

### Postdoctoral Researcher

### Heart Failure

## A NOVEL CALPAIN-2 MEDIATED REGULATION OF JUNCTOPHILIN-2 (JPH2) IN MYOCARDIAL ISCHEMIA

Satadru K Lahiri<sup>1</sup>, Hui Li<sup>2</sup>, Mohit Hulsurkar<sup>2</sup>, Hui-Bin Liu<sup>2</sup>, Ralph V Oort<sup>3</sup>, Xander Wehrens<sup>2</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX; <sup>2</sup>Cardiovascular Research Institute, Baylor College of Medicine; <sup>3</sup>Cardiology, Netherlands Heart Institute

**Background:** Junctophilin-2 (JPH2) is a membrane protein that sustains the junctional membrane complex to ensure proper excitation-contraction coupling. JPH2 cleavage by Ca<sup>2+</sup> activated proteases known as calpains is one of the main mechanisms underlying JPH2 loss in patients with ischemic heart disease contributing to contractile failure and adverse remodeling. Previous studies demonstrated that Calpain-1 mediated cleavage of JPH2 leads to nuclear translocation of one of its N-terminal fragments (JPH2-NT) which alter transcription in reducing stress-induced cardiac remodeling in mice. In our current study in the ischemia model, we identified Calpain-2 mediated novel JPH2 C terminal fragment (JPH2-CTP) which translocate to the nucleus in regulating alternative splicing and promoting adverse remodeling. Our overall hypothesis is that ischemia-induced cleavage of JPH2 by Calpain-2 leads to nuclear translocation of JPH2-CTP which further promotes maladaptive remodeling by regulating alternative splicing of critical cardiac genes.

**Materials/Methods:** We induced myocardial ischemia by ligating the left anterior descending coronary artery (LAD) in mice. We used different antibodies in western blot to assess JPH2-CTP. We further used confocal microscopy with Zeiss LSM-880 to assess JPH2-CTP localization in primary cardiomyocytes.

**Results:** We discovered novel 25-kDa JPH2-CTP to be significantly increased in myocardial ischemia. In vivo, CAPN inhibition revealed that mM Ca-activated CAPN-2 mediates JPH2 proteolysis forming CTP. Our data further reveal that a nuclear localization signal (NLS) within JPH2-CTP promotes its nuclear translocation to discrete areas identified as nuclear speckles. Mass spec followed by co-immunoprecipitation from mouse hearts after inducing ischemia revealed C1QBP, a subunit of splicing factor 2 (SF2) as a novel binding partner of JPH2-CTP. Previous studies have demonstrated that C1QBP inhibits SF2 function by preventing a stable interaction with RNA. Moreover, inhibition of SF2-mediated alternative splicing of its target genes like CaMKII $\delta$ , cardiac Troponin T, cypher, etc. alleviates maladaptive remodeling following MI. Consistent with this prior consensus, we found that nuclear JPH2-CTP alters CaMKII $\delta$  alternative splicing leading to a reduced level of 'protective' CaMKII $\delta$ B and increased levels of 'remodeling-promoting' CaMKII $\delta$ A/C isoforms following MI in WT mice but not in NLS-5A mice where the nuclear localization of CTP is blocked. We further constructed the JPH2 cleavage site deletion (CSD) knock-in mouse model which was protected from MI-induced cardiac injury compared to WT littermates.

**Conclusions:** Altogether, these findings demonstrate a novel molecular mechanism underlying CAPN2-mediated JPH2 cleavage in myocardial ischemia. Further in-depth mechanistic studies in understanding the role of this novel JPH2-CTP/C1QBP/SF2 complex in modulating alternative splicing of cardiac genes can establish a novel therapeutic approach to target ischemic cardiomyopathy.

## Poster Number 7

### Postdoctoral Researcher

#### Heart failure

### LOSS OF STRIATED MUSCLE PREFERENTIALLY EXPRESSED GENE (SPEG) KINASE DOMAIN 2 LEADS TO HEART FAILURE BY ABERRANT SARCOPLASMIC RETICULUM CA<sup>2+</sup> HANDLING

Yuriana Aguilar<sup>1</sup>, Christina Magyar<sup>2</sup>, Juwan Copeland<sup>2</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX

**Background:** Heart failure (HF) afflicts 6.5 million people in the United States and is associated with increased morbidity and a 5-year mortality rate of 50%. It is well recognized that altered sarcoplasmic reticulum (SR) Ca<sup>2+</sup> handling plays a key role in the development of contractile dysfunction and arrhythmias in HF. Whereas altered phosphorylation of the RyR2 Ca<sup>2+</sup> release channel promotes HF development, it remains controversial which kinases underlie these disease-associated changes. Our lab recently demonstrated that 'striated muscle preferentially expressed gene' (SPEG) is a novel kinase and binding partner of RyR2 and regulates intracellular Ca<sup>2+</sup> dynamics. However, the role of SPEG in HF progression has not been assessed. Here we tested the hypothesis that SPEG's kinase domain 2 phosphorylates S2367 on RyR2, and that reduced SPEG activity accelerate the development of HF due to aberrant SR Ca<sup>2+</sup> release.

**Materials/Methods:** Our lab developed a mouse model with mutations inactivating SPEG kinase domain 1 (SK1-dead) and 2 (SK2-dead). Western blots were conducted to measure RyR2 phosphorylation levels at S2367 site of both mouse models. HF was assessed by quantifying ejection fraction from echocardiograms recorded at 3, 6, and 9 months of age. Left ventricular cardiomyocytes were isolated from SK1-dead and SK2-dead mice to assess underlying intracellular Ca<sup>2+</sup> kinetics and spontaneous Ca<sup>2+</sup> release events.

**Results:** RyR2 phosphorylation was reduced at S2367 in SK2-dead mice. We observed that SK2-dead mice developed HF at 6 months. Interestingly, Ca<sup>2+</sup> spark frequency was increased at 3 months before the onset of HF.

**Conclusions:** In this study, we show that altered SPEG regulation of RyR2 is critical in heart failure progression. Specifically, the kinase domain 2 of SPEG is critical for RyR2 phosphorylation at S2367 and its loss leads to HF by dysregulating intracellular Ca release. Thus, modulating SPEG activity or directly modifying RyR2 phosphorylation at S2367 may provide new therapeutic opportunities for the treatment of HF.

**Poster Number 8**

**Postdoctoral Researcher**

**Heart Failure**

**A NOVEL TECHNOLOGY TO MONITOR MEMBRANE PROTEINS TRAFFICKING FOR DRUG DISCOVERY AND DRUG DEVELOPMENT OF CARDIOVASCULAR DISEASES AND COVID-19**

Arfaxad Reyes-Alcaraz<sup>1</sup>, Luay Boulahouache<sup>1</sup>, Elizabeth A. Merlinsky<sup>1</sup>, Bradley K. McConnell<sup>1</sup>

<sup>1</sup>College of Pharmacy, University of Houston, Houston, TX

**Background:** In cardiomyocytes, membrane proteins serve as critical signalling receptors, Ca<sup>2+</sup> cycling regulators, and electrical propagation regulators, all functioning in concert to maintain spontaneous and synchronous contractions of cardiomyocytes. Critical gene transcription and protein translation occur continuously, as well as trafficking and localization of proteins to specific functional zones of the cell membrane. However, membrane proteins are challenging to study under physiological conditions given their low endogenous expression levels. Current technologies that monitor internalization are costly and limited to a specific internalization mechanism.

**Materials/Methods:** We used high sensitive blue bioluminescence and a specific tagging system known as NanoBiT technology to study the trafficking of receptors of high relevance in cardiac diseases such as Adrenergic receptors. We also adapted our technology to study SARS-CoV2 infection in living cardiomyocytes by using blue light emission as a read out.

**Results:** By using this novel approach we were able to quantify in real-time, cardiac receptor internalization and recycling in living cells. We also were able to monitor the kinetics of SARS-CoV2 viral entry into living cardiomyocytes.

**Conclusions:** This technology can universally be applied towards a wide range of membrane proteins and used in the elucidation of novel molecular mechanisms as well as the development of therapeutic agents for several cardiac diseases, including COVID-19 mediated cardiac complications.

## Poster Number 9

### Student

### Heart Failure

#### LEFT ATRIAL FUNCTION ASSESSMENT IN OLD MALE AND FEMALE C57BL6 MICE

Jesus Ortiz Urbina<sup>1</sup>, George E. Taffet<sup>1</sup>

<sup>1</sup>Medicine-Geriatrics, Baylor College of Medicine, Houston, TX

**Background:** Aging is a major risk factor for heart failure with preserved ejection fraction (HFpEF). Left atrial dysfunction has been proposed as a contributor to HFpEF.

**Materials/Methods:** We performed two-dimensional (2D) and M-mode imaging of left atria (LA) in old male and female mice (n =18, n= 15) under 1.5% isoflurane. LA volume (V) was calculated as a prolate ellipse. Simpson's area of the LA was measured at the P wave and QRS complex marking end-systole and end-diastole. LA stroke volume (LASV), LA emptying fraction (LAEF) and LA functional index (LAFI) were derived. All animal procedures were approved by IACUC at BCM.

**Results:** LAV was significantly higher in old male mice compared to old female mice (p=0.0001), even after adjusting for body surface area (p =0.001). LASV was higher in old male mice compared to females (p =0.0001) and that persisted even after BSA adjustment (p=0.0005). LAEF and LAFI were not different between the old females and old males.

**Conclusions:** In the past, we have shown an increase in LAV to be a surrogate marker for left ventricular diastolic dysfunction in old mice. Age-related increases in LASV suggest a greater contribution of atrial contraction to left ventricular filling to compensate for worsening LV diastolic function in males more than females. Hence, LASV may be a potential target for interventions to mitigate diastolic dysfunction in aging mice.

## Poster Number 10

### Student

### Heart Failure

#### KOVACS MODELING OF DIASTOLIC FUNCTION IDENTIFIES SEX-DEPENDENT FEATURES OF CARDIAC AGING IN C57BL6 MICE

Jesus Ortiz Urbina<sup>1</sup>, Rodrigo Diaz Lankenau<sup>1</sup>, Thuy T Pham<sup>1</sup>, Mark E Entman<sup>2</sup>, George E Taffet<sup>1</sup>

<sup>1</sup>Medicine-Geriatrics, Baylor College of Medicine, Houston, TX; <sup>2</sup>Medicine-Cardiovascular Sciences, Baylor College of Medicine

**Background:** Heart failure with preserved ejection fraction (HFpEF) is predominantly a disease of older women. The aim of this study was to determine whether diastolic properties were altered by aging and sex in C57BL6 mice using Kovacs mathematical modelling.

**Materials/Methods:** Mitral Doppler imaging was performed in young (n = 8, n = 8) and old (n = 20, n = 22) C57BL6 mice of both sexes under 1.5% isoflurane. Zatebradine (0.005 mg/g) was injected to slow down the heart rate to acquire an accurate separation of E and A waves. Fitting diastole for equations of a damped spring using MATLAB was performed in five E-waves per mouse. Group comparisons were made using the T-test. All animal procedures were approved by IACUC at BCM.

**Results:** Old male mice had increases in the “spring constant” (K) ( $p = 0.02$ ) compared to young males. Old female mice were found to have a significantly larger “damping constant” (C) compared to young females ( $p = 0.01$ ). Old males had significant larger C values ( $p = 0.01$ ) than the old females.

**Conclusions:** In the Kovacs model “damping” and “spring” constants represent distinct forces acting during diastole. Our data suggest that cardiac aging might impact diastolic function differently between sexes, and therapeutic approaches might need to be different for males and females. The biochemical mechanisms for these differences are uncertain and remain an area of active investigation.



## Poster Number 11

### Clinical Fellow

### Heart Failure

#### ASSESSMENT OF MICROBIAL ETIOLOGIES OF LVAD INFECTIONS TO GUIDE DEVELOPMENT OF BACTERIOPHAGE THERAPY

Ishan Kamat<sup>1</sup>, Harveen Lamba<sup>2</sup>, Casey Hines-Munson<sup>3</sup>, Samuel Hudson<sup>3</sup>, Kenneth Muldrew<sup>4</sup>, Sabrina Green<sup>3</sup>, Austin Terwillinger<sup>3</sup>, Heidi Kaplan<sup>5</sup>, Anthony Maresso<sup>3</sup>, Barbara W. Trautner<sup>2</sup>

<sup>1</sup>Departments of Medicine, Surgery, Molecular Virology and Microbiology Pathology and Immunology, Baylor College of Medicine, Baylor College of Medicine, Houston, TX; <sup>2</sup>Department of Microbiology and Molecular Genetics, University of Texas Health Science Center at Houston

**Background:** Ventricular-assist device (VAD) infection is a common complication. To initiate development of bacteriophage therapy for VAD infections, we isolated, quantified, and categorized bacterial pathogens from retrospective and prospective cohorts of patients with VAD infections.

**Materials/Methods:** The study populations were: 1) a retrospective cohort of patients who received VADs (Nov 2003 to Aug 2017), and 2) a prospective cohort of microbial isolates from DLIs (Sept 2018 to May 2019). There were three categories: DLI, bacteremia, and device infection. We also isolated or evolved phage, evaluating lysing ability against the prospectively collected organisms.

**Results:** In the retrospective cohort, 186 of 572 patients (32.5%) developed VAD infection from 372 bacterial strains. Among these patients, 148 had DLIs, 83 had bacteremia, and 93 patients had device infections. Among the prospective isolates, 96 microbes were isolated from 54 unique VAD infections. *S. aureus* was the most common organism in both cohorts. The percentage of infections caused by gram-positive and gram-negative bacteria was similar between both cohorts,  $P = 0.3$ . We isolated and/or evolved 3 phage with ability to lyse 5 of 6 of the biofilm-producing *S. aureus* strains.

**Conclusions:** In this study, similar pathogens caused DLIs between both populations, implying that our bacterial strain bank will be representative of future DLIs. We plan to develop phage cocktails that can cover 85% or more of the organisms causing VAD infections in our institution.

## Poster Number 12

### Student

### Heart Failure

#### EXAMINING THE ROLE OF EXTRACELLULAR VESICLES IN BLOOD PRESSURE REGULATION

Feiya Shi<sup>1</sup>, Huanan Shi<sup>2</sup>, Sharon Phillips<sup>2</sup>, Bojun Zhang<sup>2</sup>, Sriram Ayyaswamy<sup>2</sup>, Robert Bryan<sup>2</sup>, David Durgan<sup>2</sup>

<sup>1</sup>Anesthesiology, Baylor College of Medicine, Houston, TX

**Background:** The gut microbiota is known to play a causal role in the pathogenesis of hypertension. However, the mechanisms by which the microbiota influences host blood pressure are largely unknown. We hypothesized that extracellular vesicles (EVs) act as mediators between the gut microbiota and host, exerting bidirectional effects to regulate blood pressure.

**Materials/Methods:** For our experiments, we used the spontaneously hypertensive stroke prone rat (SHRSP) and its normotensive control, the Wistar-Kyoto rat (WKY). For 4 weeks, we transplanted plasma EVs from SHRSP and WKY donors into SHRSP and WKY recipients via IV injection. Systolic blood pressure (SBP) measurements were taken during treatment, and flow cytometry was performed upon study completion.

**Results:** In SHRSP, WKY-EVs had a statistically significant SBP lowering effect over time compared with SHRSP-EVs. In WKY, EV type had a significant main effect on SBP, with those receiving SHRSP-EVs exhibiting elevated SBP. Flow cytometry analysis revealed that SHRSP that received SHRSP-EVs had increased Th17 and decreased Treg cells in gut compared to WKY that received WKY-EVs, consistent with previous reports citing Th17 dominance as a critical factor in hypertension. WKY-EV treatment in SHR restored Th17/Treg balance in brain and gut, while SHRSP-EV treatment in WKY exacerbated Th17/Treg imbalance in gut.

**Conclusions:** Our data suggest that EVs play an important role in regulation of host blood pressure and gut inflammation, in part by alteration of the Th17/Treg balance.

**Poster Number 13**

**Postdoctoral Researcher**

**Heart Failure**

**THE CARDIAC PROTECTIVE EFFECTS OF NOVEL SYNTHETIC PAN-ESTROGEN RECEPTOR RELATED RECEPTOR AGONISTS SLU-PP-332 AND SLU-PP-915**

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**Background:** Estrogen receptor-related orphan receptors ERR $\alpha$  and ERR $\gamma$  are essential regulators for cardiac metabolism. Mice lacking ERR $\alpha$  and ERR $\gamma$  develops lethal cardiomyopathy and heart failure (HF). Therefore, activation of ERR is a potential therapeutic intervention for HF treatment. However, no natural or synthetic ERR agonist is available to demonstrate their pharmacological effect in vivo.

**Materials/Methods:** Two structurally distinct pan-ERR agonists, SLU-PP-332 (332) and SLU-PP-915 (915) were chemically synthesized. Transaortic constriction (TAC) was performed to induce heart failure in adult male mice. Cardiac function was assessed by echocardiography. In vitro study was performed in neonatal rat ventricular myocytes (NRVM).

**Results:** 332/915 treatment significantly improved cardiac function but failed to prevent cardiac hypertrophy in mouse after 6-week TAC. Moreover, 332/915 did not prevent ERK1/2 and NFAT signaling activated by phenylephrine in NRVM. RNA-seq and metabolomics data revealed that 332/915 upregulated oxidative phosphorylation and fatty acid metabolism pathway. Finally, siRNA knockdown of ERR $\gamma$ , but not ERR $\alpha$  or ERR $\beta$ , abolished most of the 332/915-induced metabolic genes transcription in NRVM.

**Conclusions:** 332/915, mainly through ERR $\gamma$ , elevate mitochondrial function and fatty acid metabolism leading to improved cardiac function in TAC-induced heart failure, suggesting ERR agonist holds potential as a heart failure therapeutic agent.

## Poster Number 14

### Student

### Heart Failure

## TNIK REGULATES DISTURBED FLOW-INDUCED ENDOTHELIAL INFLAMMATION AND PROLIFERATION THROUGH FAK-MEDIATED STAT SIGNALING

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**Background:** Atherosclerosis (AS) is the major cause of CVD. AS develops at disturbed flow (DF) regions. Endothelial cell (EC) activation and inflammation, the first step of AS, is triggered by DF. Understanding the mechanisms of EC inflammation is critical to prevent CVD. TNIK a kinase in the Ste20 family of MAP kinases (MAP4K) regulates the  $\beta$ -catenin/TCF4 complex. However, roles for TNIK in EC activation remain to be studied. To examine the biological implications of TNIK in ECs, we treated ECs with TNIK siRNA then the cells were exposed to physiological shear conditions and were transcriptionally profiled. We believe that this study will pave way for understanding a novel shear stress-sensitive mechanism of EC activation regulated by TNIK.

**Materials/Methods:** Cultured HAECs were first treated with control or TNIK-targeted siRNA. After cells were treated with siRNA, they were subjected to static, laminar, or disturbed flow conditions. Total RNA was isolated from these cells and RNA-sequencing was performed. The differential expression data were analyzed using CLC genomics and IPA platform (QIAGEN).

**Results:** TNIK depletion under DF leads to upregulation of integrin and eIF2 signaling while downregulating Interferon (IFN) signaling specifically STAT1,2, interferon-stimulated genes (ISGs), and hypercytokinemia. Therefore, TNIK is a potent activator of IFN responses in ECs.

**Conclusions:** We propose that TNIK can effectively regulate FAK-mediated STAT and pathway to regulate EC inflammation.

## Poster Number 15

### Junior Faculty

### Atherosclerosis

#### INHIBITION OF CASPASE-1 REDUCES MYOCARDIAL INFARCT SIZE AND POST-INFARCT LEFT VENTRICULAR REMODELING

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**Background:** Patients with acute myocardial infarction (AMI) receive revascularization and a P2Y<sub>12</sub> receptor antagonist, an intervention that reduces but does not eliminate mortality and heart failure. Injury during the ischemic phase releases Damage Associated Molecular Patterns (DAMPs), leading to inflammation involving the arachidonic acid cascade and the inflammasome-caspase-1 axis. Administration of the 20-HETE antagonist, 20-SOLA, or the caspase-1 inhibitor VX-765 at the onset of reperfusion in AMI rat models decreases infarct size and preserves ventricular function. However, cellular mechanisms underlying the inhibitor's cardioprotective effects are unknown.

**Materials/Methods:** Rats were subjected to 60 min coronary ligation/ followed by a 3-day recovery (close chest) before a final assessment. Cangrelor (60 µg, bolus I.V.) was followed by infusion (6 µg/kg/min) 10-min before reperfusion; VX-765 (32 mg/kg) or DMSO (vehicle control) were injected IV (bolus) 5-min before reperfusion.

**Results:** In untreated experimental control animals, infarction was 73.7±4.1% of the risk zone. Cangrelor in combination with DMSO (cangrelor/DMSO) decreased infarction to 63.8±4.8%. Cangrelor and VX (cangrelor/VX) decreased infarction to 17.7±1.4%. Fractional shortening was declined by 30% in untreated animals, an effect rescued by cangrelor/VX. The mechanism underlying cardioprotection was examined in a 60-min regional ischemia/30-min reperfusion to measure functional downstream effectors, while the myocardium was still viable rather than after cell death had occurred. The downstream targets for caspase-1, IL-1β, and IL-18, were decreased in the VX group in the myocardium and the circulation compared to any other group. Mitochondrial fitness was tested in ischemic and non-ischemic ventricles by respirometry (JO<sub>2</sub>). In non-ischemic and ischemic tissues, complex I activity was significantly lower in hearts treated with VX while there was an increase in complex III activity in ischemic zones. Protein carbonylation, a surrogate measure of oxidative injury, was not increased in the VX group. In a similar model of injury, administration of 20-SOLA during reperfusion rescued ATP production compared to controls.

**Conclusions:** Our data indicate that in a clinically relevant AMI model, inhibition of inflammatory pathways at the onset of reperfusion prevents bioenergetic crisis, increases myocardial survival, and maintains ventricular function.

**Poster Number 16**

**Postdoctoral Researcher**

**Atherosclerosis**

**AN UNFOLDED PROTEIN RESPONSE DRIVES CHOLESTEROL-INDUCED PHENOTYPIC MODULATION OF SMOOTH MUSCLE CELLS TO MACROPHAGE/FIBROBLAST-LIKE CELLS**

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**Background:** When exposed to cholesterol, vascular smooth muscle cells (SMCs) undergo phenotypic modulation, wherein they dedifferentiate and initiate expression of macrophage and fibroblast markers. This phenotypic switching to a pro-atherogenic cell is dependent on Krüppel-like factor 4 (Klf4).

**Materials/Methods:** By exposing SMCs to free cholesterol in culture, we investigated the molecular pathway by which cholesterol induces SMC phenotypic modulation.

**Results:** Cholesterol exposure decreases SMC contractile marker expression, activates Klf4 and upregulates a subset of macrophage and fibroblast markers characteristic of modulated SMCs (mSMCs) that appear with atherosclerotic plaque formation. These phenotypic changes are associated with activation of all 3 pathways of the endoplasmic reticulum (ER) unfolded protein response (UPR): Perk, Ire1 $\alpha$  and Atf6. Inhibiting the movement of cholesterol from the plasma membrane to the ER prevents this phenotypic modulation, as does global UPR inhibition or specific inhibition of Perk signaling. Exposure to chemical UPR inducers, tunicamycin and thapsigargin, is sufficient to induce these same phenotypic transitions. Finally, analysis of single cell RNA sequencing data during atherosclerotic plaque formation in hyperlipidemic mice provides preliminary in vivo evidence of a role of UPR activation in mSMCs.

**Conclusions:** Our data demonstrate that UPR is necessary and sufficient to drive phenotypic switching of SMCs to cells that resemble modulated SMCs found in atherosclerotic plaques.



## Poster Number 17

### Student

### Atherosclerosis

#### ROS INDUCED MITOCHONDRIAL DYSFUNCTION IS INDEPENDENT OF THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE

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**Background:** Over 750,000 Americans suffer a myocardial infarction (MI) every year, the major contributing factor for heart disease related mortalities. During ischemia and subsequent reperfusion, cardiomyocytes are exposed to toxic levels of Ca<sup>2+</sup> and reactive oxygen species (ROS) which induce cell death through mitochondrial permeability transition pore (MPTP) opening. The mechanism of how these stimuli converge on the same pore to induce mitochondrial dysfunction remains unknown. Here, we investigate the mechanisms of how Ca<sup>2+</sup> and ROS induce mitochondrial dysfunction.

**Materials/Methods:** We performed fluorometric assays, the mitochondrial Ca<sup>2+</sup> retention capacity and swelling assays, with Ca<sup>2+</sup>, Fe<sup>2+</sup>, t-butyl H<sub>2</sub>O<sub>2</sub> with/without MPTP inhibitors. We also visualized isolated mitochondria by transmission electron microscopy (TEM) using similar inducers of dysfunction.

**Results:** MPTP-specific inhibitors prevented Ca<sup>2+</sup>-induced mitochondrial swelling but not Fe<sup>2+</sup> and H<sub>2</sub>O<sub>2</sub>-induced swelling, suggesting that the MPTP is not triggered by ROS. Furthermore, a lipid peroxidation inhibitor, ferrostatin-1 (Fer-1), inhibits mitochondrial dysfunction induced by Fe<sup>2+</sup> and H<sub>2</sub>O<sub>2</sub>. In addition, Ca<sup>2+</sup> and Fe<sup>2+</sup> induce unique mitochondrial cristae remodeling observed by TEM.

**Conclusions:** Ca<sup>2+</sup> and ROS elicit distinct forms of mitochondrial dysfunction, and we plan to assess the efficacy of dual inhibition of these forms against I/R injury in mice. We predict that dual inhibition will be additively protective in reducing cardiomyocyte death and infarct size.

**Poster Number 18**

**Junior Faculty**

**Atherosclerosis**

**CHANGE IN PLASMA HOMOCYSTEINE AND OXIDIZED LDL LEVELS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING: A COMPARISON BETWEEN MEDIAN STERNOTOMY AND ROBOTIC-ASSISTED MINI-THORACOTOMY APPROACH**

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**Background:** Elevated plasma homocysteine (Hcy) and oxidized low-density lipoproteins (OxLDL) are associated not only with thrombo-embolic complications, but also with increased morbidity and mortality in patients undergoing cardiac surgery. We hypothesized that robotic-assisted minimally invasive coronary artery bypass (Robotic CABG) impacts the plasma Hcy and OxLDL burden in patients differently when compared to conventional coronary artery bypass graft (Open CABG).

**Materials/Methods:** Pre-, intra- and post-operative blood samples were collected from each patient. Blood from healthy volunteers were also collected as controls. Total Hcy and OxLDL in plasma were measured.

**Results:** At baseline; both Open-CABG and Robotic-CABG patients had higher plasma Hcy and OxLDL than controls. Intraoperative plasma levels of Hcy and OxLDL were significantly increased in both Open-CABG and Robotic-CABG patients compared to preoperative. Postoperatively, Hcy and OxLDL levels returned to baseline within a week in Robotic-CABG, but remained elevated in the Open-CABG.

**Conclusions:** Elevated Hcy, OxLDL were indicators of systemic response of the body during cardiac surgery. Positive association between Hcy and OxLDL indicated that the elevated Hcy may act as an atherogenic factor by promoting oxidative stress. The quicker return-to-normal of these markers after surgery in Robotic CABG patients suggests a lesser systemic impact from surgery when compared to Open CABG. Decreased marker levels in Robotic-CABG might correlate to improved clinical outcomes.

**Poster Number 19**

**Junior Faculty**

**Atherosclerosis**

**STEROID RECEPTOR COACTIVATOR STIMULATOR (MCB-613)-BASED IMMUNOMODULATION ATTENUATES PROGRESSION TO HEART FAILURE BY REDUCING INFLAMMATION-RELATED CARDIAC FIBROSIS AND IMPROVED REMODELING AFTER MI**

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**Background:** Few interventions exist to target the underlying mechanisms that drive post-MI chronic heart failure. Recently our laboratory published that stimulation of Steroid Receptor Coactivators (SRCs) with MCB-613 can preserve ejection fraction and significantly attenuate chronic pathologic remodeling after MI. We now identified the cell-type specific responses responsible for MCB-613's cardio-protective effects.

**Materials/Methods:** Single cell transcriptomics of cardiac interstitial cells were performed at the inflammatory phase (24 hours) and the maturation phase (12 weeks) post-MI to reveal the post-MI cell types and transcriptional responses associated with improved cardiac function in response to SRC-3 activation. We measured the effect of MCB-613 on immune cells and fibroblasts in vitro.

**Results:** Early protection was concomitant with: (i) inhibition of macrophage inflammatory signaling and IL-1 signaling, (ii) attenuation of fibroblast differentiation, and (iii) promotion of Tsc22d3 expressing macrophages. Analysis at 12 weeks revealed enrichment of matrifibrocyte scar-specific fibroblasts that underlie the long-term stability of the fibrotic scar. In vitro data show that MCB-613 stimulation suppresses IL-1 signaling in macrophages, neutrophils and fibroblasts and enhances iBreg and iTreg (immunoregulatory cell) polarization.

**Conclusions:** Immunomodulation of early paracrine signaling by SRC activation represents a potential novel therapeutic option for promoting 'improved fibroblast and cardiac remodeling' after MI.

## Poster Number 20

### Junior Faculty

#### Atherosclerosis

### INHIBITION OF 20-HETE REDUCES MYOCARDIAL INFARCT SIZE AND POST INFARCT LEFT VENTRICULAR REMODELING

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**Background:** 20-hydroxyeicosatetraenoic acid (20-HETE) may be a mediator of myocardial ischemia-reperfusion injury. Studies to date are limited by short-term follow up and administration of inhibitors prior to onset of ischemia.

**Materials/Methods:** We evaluated the effect of a 20-HETE antagonist, 20-SOLA, administered at onset of reperfusion, on left ventricular (LV) remodeling 48 hours and 8 weeks after myocardial infarction (MI) in normal (SD) and metabolic syndrome (JCR) rats.

**Results:** MI size was markedly greater in JCR vs. SD rats at 48 hours of reperfusion (86 $\pm$ 4% vs. 25 $\pm$ 6% of risk zone). 20-SOLA significantly decreased MI size in SD (10 $\pm$ 5% of risk zone) and JCR (16 $\pm$ 3% of risk zone) rats, which was associated with improved coronary blood flow. Smaller MIs in 20-SOLA-treated JCR rats also correlated with decreased neutrophils, superoxide and IL-6. LV function was preserved 8 weeks post MI in 20-SOLA-treated animals (ejection fraction=81.3 $\pm$ 4.5% (SD+20-SOLA) and 83.5% (JCR+20-SOLA) vs. 57.5 $\pm$ 4.5% (SD) and 34.2 $\pm$ 2.5% (JCR)). This correlated with preserved myocyte morphology, intact collagen, decreased apoptosis and differential activation of matrix metalloproteinases. Moreover, preserved LV function in 20-SOLA-treated animals correlated with markedly decreased mortality (survival was 31% and 71% in untreated JCR and SD vs. 100% in 20-SOLA-treated animals).

**Conclusions:** These results indicate that inhibition of 20-HETE may be an important consideration in preventing long-term LV remodeling and mortality post MI.

## Poster Number 21

### Junior Faculty

### Atherosclerosis

#### **DYNAMIC EFFECTS OF GENETIC VARIATION ON GENE EXPRESSION REVEALED FOLLOWING HYPOXIC STRESS IN CARDIOMYOCYTES**

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**Background:** Myocardial infarction (MI) deprives cardiomyocytes of oxygen. Susceptibility to MI varies between individuals, and treatment can lead to secondary effects such as ischemia-reperfusion injury in a subset of patients. We sought to gain insight into inter-individual genetic effects on the response to and from hypoxia in human cardiomyocytes.

**Materials/Methods:** We generated induced pluripotent stem cell-derived cardiomyocytes from 15 healthy genotyped individuals. We characterized gene expression levels, chromatin accessibility, and methylation profiles in these cardiomyocytes under normoxia, hypoxia, and short or long-term re-oxygenation.

**Results:** 2,113 genes change their expression following hypoxia and short- or long-term re-oxygenation. We identified 1,573 genes whose expression levels associate with the presence of a particular genetic variant - expression quantitative trait loci (eQTLs) - in at least one condition. We also identified 367 dynamic eQTLs, which are classified as eQTLs in at least one, but not in all conditions. A subset of dynamic eQTLs have not been previously annotated as eQTLs even in much larger collections of heart tissues. We observed minimal changes in DNA methylation and chromatin accessibility following hypoxia. Finally, we found that genes associated with dynamic eQTLs are also associated with coronary artery disease and MI.

**Conclusions:** Our data demonstrate how dynamic genetic effects on gene expression, which are likely relevant for disease, can be uncovered under conditions of stress.

**Poster Number 22**

**Postdoctoral Researcher**

**Aortopathy**

**TBK1 MEDIATES METABOLIC REWIRING IN M1 MACROPHAGE BY PHOSPHORYLATING PYRUVATE DEHYDROGENASE-POTENTIAL IMPLICATION IN AORTIC INFLAMMATION**

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**Background:** Macrophage infiltration in the aortic wall is a key pathological feature of aortic aneurysm and dissection (AAD). Macrophages can be polarized into pro-inflammatory (M1) and pro-healing (M2) macrophages. In this study, we examined macrophage polarization in AAD and the mechanisms involved in this process.

**Materials/Methods:** Single-cell RNA seq analysis was combined with in vitro kinase assay, co-IP assay to identify the key mechanism of metabolism change in macrophages.

**Results:** In human AAD tissue, single-cell RNA sequencing analysis revealed significant M1 polarization that was associated with higher glycolysis, particularly in AAD tissues. Consistently, immunostaining of macrophages in human AAD tissue showed increased phosphorylation/inactivation of pyruvate dehydrogenase alpha 1 (PDHA1), a key enzyme that reduces the glycolysis product lactate by promoting pyruvate into the TCA cycle. PDHA1 phosphorylation in macrophages was associated with increased expression of proinflammatory kinase TANK-binding kinase (TBK1). In cultured macrophages, TBK1 directly bound and phosphorylated PDHA1 at multiple sites. Silencing TBK1 prevented PDHA1 phosphorylation and lactate production.

**Conclusions:** Our results demonstrated significant M1 polarization that is associated with higher glycolysis in AAD tissue. Pro-inflammatory TBK1 enhances glycolysis by directly phosphorylating/inhibiting PDHA1; this finding provides novel insight into how innate immune signaling rewires the metabolism of macrophages during polarization.

**Poster Number 23**

**Postdoctoral Research Trainee**

**Aortopathy**

**MITOCHONDRIAL DAMAGE CONTRIBUTES TO SMOOTH MUSCLE CELL PHENOTYPE CHANGE, AORTIC DEGENERATION, AND AORTIC ANEURYSM AND DISSECTION FORMATION THROUGH MTDNA-CGAS –STING SIGNALING**

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**Background:** The mechanisms of aortic smooth muscle cell (SMC) dysfunction in aortic aneurysm and dissection (AAD) development are poorly understood. Here, we examined the role of mitochondrial damage in aortic SMC dysfunction in sporadic AAD formation.

**Materials/Methods:** Mitochondrial damage, cytosolic mtDNA, and cGAS-STING signaling in SMCs were examined in aortic tissues from patients with sporadic ascending AAD. cGAS-deficient mice evaluated with sporadic AAD induced by high-fat diet and angiotensin II challenge. The effect of mitochondrial damage on SMC phenotype change was examined in vitro.

**Results:** In AAD aortic tissues from patients and mice, we found profound mitochondrial dysfunction and SMC damage characterized by down-regulation of mitochondrial genes in the citric acid cycle and the oxidative phosphorylation complex and by mitochondrial swelling and rupture. In cultured SMCs, mitochondrial damage caused release of cytosolic mtDNA and activation of the cGAS-STING cytosolic DNA sensor pathway, which prevented DNA repair, exacerbated mitochondrial dysfunction, and induced SMC senescence-associated secretory phenotype. In mice, deficiency of cGAS-STING signaling mitigated challenge-induced mitochondrial dysfunction, senescence and death in SMCs, reducing aortic enlargement, dissection, and rupture.

**Conclusions:** Mitochondrial DNA leak and subsequent activation of cGAS-STING signaling triggered mitochondrial dysfunction and damage that caused SMC phenotype change, leading to aortic degeneration and AAD development.



**Poster Number 24**

**Postdoctoral Researcher**

**Aortopathy**

**SINGLE-CELL ANALYSIS REVEALS PARADOXICAL TGF- $\beta$  SIGNALING AND INCREASED EXPRESSION OF ELASTIN IN THE AORTIC WALL SPECIFIC TO ASCENDING AORTIC ANEURYSMS IN PATIENTS WITH MARFAN SYNDROME**

Ashley Dawson<sup>1</sup>, Yanming Li<sup>1</sup>, Chen Zhang<sup>1</sup>, Hernan G. Vasquez<sup>1</sup>, Alon R. Azares<sup>2</sup>, Aladdein Mattar<sup>1</sup>, Joseph S. Coselli<sup>1</sup>, Alan Daugherty<sup>3</sup>, Ying H. Shen<sup>1</sup>, Scott A. LeMaire<sup>1</sup>

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**Background:** Marfan syndrome (MFS) is caused by mutations in FBN1; however, the processes leading to aneurysm formation are poorly understood. We aimed to identify changes unique to non-immune cells in MFS by comparing cell-specific gene expression in tissue from MFS and sporadic ascending aortic aneurysms (ATAAs).

**Materials/Methods:** We performed single-cell RNA sequencing of ATAA tissues from patients with MFS (n=4) and sporadic disease (n=6). Data from non-immune cells (n=9,450) were extracted for further analysis.

**Results:** Non-immune cell clusters identified by conserved gene expression included contractile SMCs (n=3), modulated SMCs (n=1), immature SMCs (n=3), fibroblasts (n=1), and endothelial cells (ECs; n=2). FBN1 was downregulated and ELN was upregulated in MFS compared to sporadic tissues in fibroblasts. Within TGF- $\beta$  signaling, TGFB1 was most highly expressed in fibroblasts and upregulated in MFS. TGF- $\beta$  receptors and downstream SMAD genes were downregulated in MFS compared to sporadic ATAA tissue in fibroblasts, SMCs, and ECs. These differences were not seen in nonaneurysmal tissues between younger and older controls, suggesting these findings related to pathology rather than age differences in patients with MFS and sporadic ATAA.

**Conclusions:** Upregulation of TGFB1 in fibroblasts without associated upregulation of downstream TGF- $\beta$  signaling is specific to ATAA in MFS. Upregulation of elastin-associated genes may indicate a compensatory response to the FBN1 mutation rather than a response to aortic wall stress.

**Poster Number 25**

**Postdoctoral Researcher**

**Aortopathy**

**SINGLE-CELL RNA SEQUENCING OF ANEURYSMAL ASCENDING AORTIC TISSUE REVEALS EVIDENCE OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH MARFAN SYNDROME**

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**Background:** Changes in the aortic wall leading to ascending thoracic aortic aneurysms (ATAAs) in patients with Marfan syndrome (MFS) are poorly understood. As aortic endothelial cells (ECs) are vital in maintaining a normal aortic wall, we hypothesized that ECs in MFS would show evidence of dysfunction when compared with control tissue.

**Materials/Methods:** We performed single-cell RNA sequencing of ATAA tissues from patients with MFS (n=3) and of age-matched control tissues (n=4). Data from ECs (n=2,218) were extracted for further analysis.

**Results:** We identified 11 clusters of ECs including normal ECs (n=3), ECs involved in vascular healing/angiogenesis (n=3), inflammation (n=2), development (n=2), and smooth muscle cell-like ECs (n=1). Tight and adherens junction gene expression was highest in vascular healing ECs and CLDN5, the predominant tight junction gene expressed in our data, was decreased in MFS in this cluster. Vascular healing ECs were increased in MFS compared to control tissues and showed upregulation of genes involved in vasculogenesis in MFS tissue on Gene Ontology analysis.

**Conclusions:** MFS tissues had a higher proportion of ECs involved in maintaining the endothelial barrier but decreased expression of the predominant tight junction gene CLDN5. Genes involved in vasculogenesis were also significantly upregulated in MFS tissue. These findings suggest dysfunction of the endothelial barrier in MFS with a potential compensatory response.

**Poster Number 26**

**Student**

**Aortopathy**

**ABSENCE OF THORACIC AORTIC DISEASE IN ACTA2R149C/+ MICE IS ASSOCIATED WITH DEFECTIVE RELEASE OF MUTANT SMOOTH MUSCLE A-ACTIN FROM THE CHAPERONIN COMPLEX**

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**Background:** Pathogenic variants in ACTA2 (smooth muscle  $\alpha$ -actin) predispose to heritable thoracic aortic aneurysms and dissections. ACTA2 R149C is the most common alteration however only 60% of carriers have a dissection or aneurysm repair by age 70. We sought to determine how ACTA2 R149C causes aortic disease.

**Materials/Methods:** The Acta2R149C/+ mouse model was generated using CRISPR/Cas9 technology. Smooth muscle cells (SMCs) were explanted from wild type (WT) and mutant mice. In vitro studies were used to assess actin filament dynamics.

**Results:** Acta2R149C/+ mice had significantly decreased aortic contraction compared to WT mice but did not form aortic aneurysms or dissections. Increasing biomechanical forces on the ascending aorta did not induce aortic disease in the Acta2R149C/+ mice. In vitro studies found decreased interaction of the mutant SM  $\alpha$ -actin filament with myosin motors and enhanced interaction of mutant SM  $\alpha$ -actin with formin, leading to altered SM  $\alpha$ -actin filaments in SMCs. However, the most prominent molecular defect was increased retention of mutant  $\alpha$ -actin in the CCT folding complex, which reduced mutant versus WT SM  $\alpha$ -actin levels in Acta2R149C/+ SMCs.

**Conclusions:** These data indicate that Acta2R149C/+ mice do not develop aortic disease despite decreased contraction of aortic segments and disrupted mutant SM  $\alpha$ -actin filaments. Enhanced binding of mutant SM  $\alpha$ -actin to CCT may decrease the mutant actin monomer available for cellular functions in SMCs and prevent thoracic aortic disease in the Acta2R149C/+ mice.

Poster Number 27

Postdoctoral Researcher

Aortopathy

## **SEX-SPECIFIC DNA METHYLATION AND EXPRESSION PROFILES OF X-CHROMOSOME GENES IN HUMAN AORTIC SMOOTH MUSCLE CELLS**

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**Background:** The incidence and progression of thoracic aortic aneurysm and dissection differ between sexes. Understanding the molecular mechanisms underlying these differences is important for developing sex-specific treatments. We hypothesized that variations in the epigenetic regulation of X-chromosome genes in women modulate susceptibility to sporadic ascending thoracic aortic aneurysm (ATAA) development and disease progression.

**Materials/Methods:** We extracted DNA and RNA from the medial layer (predominantly smooth muscle cells) of the ascending aorta from 4 age- and ethnicity-matched groups (men with aneurysm, women with aneurysm, control men, control women) and performed DNA methylation analysis and bulk RNA sequencing.

**Results:** Aneurysm tissues from women with aneurysm showed patterns of DNA methylation and gene expression that were different from those of other groups. Sex-specific differential expression and methylation of X-chromosome genes were observed between aneurysm and control tissues. In women only, expression of the X-chromosome gene anti-apoptosis molecule brain expressed X-linked 2 (BEX2) was lower in aneurysm tissues than in control tissues. Additionally, aortic BEX2 expression was slightly higher in control women than in control men. Decreased BEX2 expression in aneurysm tissues from women was associated with increased promoter methylation.

**Conclusions:** The epigenetic regulation of X-chromosome gene expression in the aorta may contribute to ATAA development in women.

**Poster Number 28**

**Postdoctoral Researcher**

**Aortopathy**

**SINGLE-CELL RNA SEQUENCING REVEALS THE HETEROGENEITY OF AORTIC FIBROBLASTS DURING AORTIC DISEASE DEVELOPMENT IN MICE**

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**Background:** Aortic fibroblasts are critical in repair and remodeling in aortic aneurysm and dissection (AAD), but their molecular and cellular changes during AAD development are poorly understood. Here, we used single-cell RNA sequencing to examine aortic fibroblast heterogeneity in a sporadic AAD mouse model.

**Materials/Methods:** Wild-type mice were unchallenged or challenged with a high-fat diet and angiotensin II infusion. We generated single-cell suspensions for scRNA-seq from thoracic aortas and analyzed 16,187 cells by using the Seurat, edgeR, and Monocle package in R.

**Results:** We identified 7 aortic fibroblast subsets: extracellular matrix (ECM) fibroblasts, myofibroblasts, Tnfrsf11bhigh fibroblasts, 2 clusters of mesenchymal progenitor cells (MPCs), pro-inflammatory fibroblasts, and Cd14+ fibroblasts. These subsets showed specific gene expression patterns indicating their putative functions (eg, increased collagen synthesis and ECM organization in ECM fibroblasts, increased proliferation, and migration in Tnfrsf11bhigh and pro-inflammatory fibroblasts, and increased cell adhesion and cell junction organization in myofibroblasts and MPCs). Pseudotime analyses suggested Tnfrsf11b is important in fibroblast trajectory differentiation. Pro-inflammatory and Cd14+ fibroblasts were found almost exclusively in challenged mice.

**Conclusions:** Aortic fibroblasts showed marked phenotypic heterogeneity and changes in gene expression during aortic stress, suggesting specialized functions of fibroblast subsets.

## Poster Number 29

### Student

### Arrhythmia

## ROLE OF JUNCTOPHILIN-2 IN THE CARDIAC CONDUCTION SYSTEM

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**Background:** Hypertrophic cardiomyopathy (HCM), occurring ~0.2%-0.3% in the general adult population, is a genetic disorder of cardiac muscle characterized by left ventricular hypertrophy and in certain cases sudden cardiac death. HCM can be caused by mutations in Junctophilin-2 (JPH2). JPH2 is a structural Ca<sup>2+</sup> handling protein that interacts with the voltage-gated Ca<sup>2+</sup> channels and ryanodine receptors. Studies have indicated that HCM due to JPH2 mutations in humans are associated with disease in the cardiac conduction system (CCS). However, the role of JPH2 in the CCS has not been studied before.

**Materials/Methods:** Floxed-shJPH2 mice were crossed with HCN4-Cre (Cre driven by CCS specific promoter HCN4) mice, where Cre recombinase promotes shRNA mediated JPH2 knockdown in the CCS specifically. Surface ECG and intracardiac electrogram were performed in these CCS-specific JPH2 knockdown mice. Mice with JPH2 mutation A399S (corresponding to human HCM patients with JPH2 A405S mutation) and truncating variant JPH2 E640X were assessed by echocardiography, surface EKG, and intracardiac electrogram. JPH2 expression level was assessed in JPH2 E640X mice by Western Blot.

**Results:** Mice heterozygous for A399S developed hypertrophy mainly in the interventricular septum, which is a phenotype similar to human variant carriers. Interestingly, these mice also developed significant atrioventricular (AV) block prior to the HCM phenotype. Another JPH2 mouse model harboring the E640X human variant, which had reduced JPH2 expression, developed conduction diseases such as AV block and QRS widening. To further assess the role of JPH2 in the CCS specifically, intracardiac electrogram and surface EKG studies in the HCN4-Cre:shJPH2 mice revealed significant AV block and QRS widening following CCS-specific JPH2 knockdown, further strengthening our hypothesis that JPH2 plays an essential role in maintaining normal cardiac conduction.

**Conclusions:** Our study suggests that the normal function of JPH2 is critical for cardiac conduction through the His-Purkinje system. JPH2 loss-of-function may account for the CCS abnormality in HCM, likely through its impaired role on Ca<sup>2+</sup> handling at the junctional membrane complex, either by JPH2 dysfunction or by the decreased expression level of JPH2.

**Poster Number 30**

**Postdoctoral Researcher**

**Arrhythmia**

### **GASDERMIN D PROMOTES ATRIAL ARRHYTHMOGENESIS**

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**Background:** Gasdermin D (GSDMD) is a downstream effector of NLRP3 inflammasome. Cleaved N-terminal GSDMD (GSDMDNT) facilitates the release of IL-1 $\beta$  from immune cells and lytic cell death (known as pyroptosis). The function of GSDMD in cardiomyocytes (CMs) is less known. In the atria of patients with atrial fibrillation (AF), GSDMDNT level was increased. Thus, we sought to evaluate the specific function of CM GSDMD and the causal role of GSDMDNT in AF development.

**Materials/Methods:** To establish the mouse model with atrial CM-specific overexpression of GSDMDNT, we injected 6-week C57BL6/J mice with atrial-specific AAV9-ANF-GSDMDNT vectors (aGSDMDNT) or AAV9-ANF-Flag (aCtl).

**Results:** Western blots revealed GSDMDNT level was higher in human atrial CMs of AF patients and in atria of aGSDMDNT mice. Programmed intracardiac simulation revealed aGSDMDNT mice were more susceptible to AF-induction. Optical mapping study showed a reduced atrial effective refractory period, suggesting aGSDMDNT mice developed electrical remodeling. Interestingly, the LDH level (a marker of pyroptosis) was unchanged, suggesting CM GSDMDNT exhibited unique functions unrelated to pyroptosis. Lastly, NLRP3 inflammasome activation was enhanced in atria of aGSDMDNT mice, forming a feedforward loop between GSDMDNT and NLRP3 inflammasome activation.

**Conclusions:** Our study suggests that GSDMDNT exhibits pyroptosis-independent function that can enhance AF susceptibility. Future studies will determine the molecular mechanisms of GSDMDNT-mediated atrial arrhythmogenesis.



**Poster Number 31**

**Postdoctoral Researcher**

**Arrhythmia**

**ATRIAL-SPECIFIC LKB1 KNOCKDOWN REPRESENTS A NOVEL MOUSE MODEL OF ATRIAL CARDIOMYOPATHY WITH SPONTANEOUS ATRIAL FIBRILLATION**

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**Background:** AF is the most common cardiac arrhythmia with > 37 MM patients. To develop effective therapies, it is essential to uncover underlying mechanisms using better models. Liver kinase b1 (Lkb1) knockout mice develop spontaneous AF by 8 weeks. Main limitation of this model is ventricular dysfunction and heart failure, complicating the understanding of mechanisms. Our objective was to develop an atrial specific model of spontaneous AF without confounding ventricular effects.

**Materials/Methods:** We used the AAV9-ANF-Cre to drive atrial-specific Lkb1-knockdown (Lkb1-aKD) following injection into 5-day-old LKB1FL/FL mice. 24-hours ECGs were obtained once/week via subcutaneously implanted telemeters. AF was defined by a lack of P-waves and irregularly irregular R-R intervals for more than 10 second.

**Results:** Lkb1-aKD mice exhibited 80% AF incidence at 8 weeks and an age-dependent increase in the duration of spontaneous AF episodes. Increased atrial size and diminished mitral valve function indicated increased atrial cardiomyopathy. No change was seen in LVEF in 12 weeks old LKB1-aKD mice. Lkb1 downregulation was observed in atrial but not in ventricular tissue. Prominent atrial fibrosis was observed in the atria of Lkb1-aKD mice.

**Conclusions:** AAV9-mediated knockdown of Lkb1 produces a novel mouse model of AF and cardiomyopathy without ventricular remodeling. Lkb1-aKD mice represent a practical atrial-specific mouse model of spontaneous AF for mechanistic studies aimed to uncovering the molecular basis of spontaneous AF.

## Poster Number 32

### Student

### Arrhythmia

## DEFICIENCY OF THE ATRIAL FIBRILLATION RISK GENE PITX2 RESULTS IN NON-CELL AUTONOMOUS ACTIVATION OF CARDIAC FIBROBLASTS

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**Background:** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is known that reduction of Pitx2, a critical cardiac transcription factor, results in atrial arrhythmogenesis through altering transcription of ion channels in left atrial cardiomyocytes. However, the effects of Pitx2 deficiency on other cardiac cell types critical for AF pathogenesis is not established. We therefore hypothesize that non-cardiomyocytes contribute significantly to AF pathogenesis in cardiac Pitx2 deficiency.

**Materials/Methods:** Single-cell RNA sequencing and bulk RNA sequencing were used to discover alterations in left atrial gene expression in multiple mouse models of Pitx2 deficiency. These datasets were integrated to determine Pitx2 target genes, which were then functionally validated in vivo using mouse genetics.

**Results:** Single-cell RNA sequencing revealed activation of Pitx2 mutant cardiac fibroblasts (CFs). Bulk RNA sequencing then confirmed upregulation of multiple fibroblast activation genes in Pitx2<sup>null/+</sup> left atrium. Integration these datasets revealed increased Wnt signaling in the mutant CFs, which was confirmed using an in vivo Wnt reporter allele.

**Conclusions:** We conclude that cardiac Pitx2 deficiency results in CF activation. Current therapies for AF focus extensively on restoring regular electrical conduction with medication or ablation of ectopic tissue. Our long-term goal is to broaden the therapeutic approaches for AF treatment by continuing to explore this novel mechanism of fibroblast activation.

**Poster Number 33**

**Postdoctoral Researcher**

**Arrhythmia**

**SINGLE-CELL, MULTIOMICS APPROACH TO PITX2 IN ATRIAL FIBRILLATION**

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**Background:** Atrial fibrillation (AF), the most common cardiac arrhythmia and a major risk factor for stroke, occurs when ectopic electrical impulses originating from the pulmonary vein (PV) and atria trigger cardiac depolarization that compete with sinus rhythm. Patient data and animal models overwhelmingly implicate the transcription factor PITX2, expressed in the cardiomyocytes (CMs) of the developing left atrium (LA) and PV, in predisposition to AF. To understand the molecular drivers of AF, it is imperative to understand the transcriptional and epigenetic targets of PITX2.

**Materials/Methods:** In this study, we performed multiomic profiling of LA and PV single nuclei from adult Pitx2 control and mutant mice.

**Results:** We identified three populations of CMs, two of which are enriched in the PV, and our associated with different sets of AF-associated gene expression. Pitx2 mutant CMs exhibit changes in gene expression consistent with arrhythmia and appear to be in a direct PITX2-dependent manner through interaction with a predicted set of core transcription factors. Furthermore, changes in the CMs appear to have a direct impact on the endocardium/endothelium of the LA and PV through changes in CM-derived signaling.

**Conclusions:** Through this work, we have begun laying the groundwork to understand the direct molecular mechanisms governed by Pitx2 in the LA/PV CMs. In the future, we plan to identify the molecular machinery by which PITX2 interacts to govern the cis-regulatory landscape of the LA and PV myocardium in disease context.

**Poster Number 34**

**Postdoctoral Researcher**

**Arrhythmia**

**FKBP5 DEFICIENCY LEADS TO ATRIAL ARRHYTHMOGENESIS**

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**Background:** Atrial fibrillation (AF) is the most common arrhythmia. Recent transcriptome study FK506 binding protein 5 (FKBP5) gene was downregulated in atria of AF patients. In this study, we tested the hypothesis that FKBP5 deficiency promotes atrial arrhythmogenesis.

**Materials/Methods:** FKBP5 protein level was assessed in atrial tissues of patients with normal sinus rhythm (NSR) and long-lasting persistent (chronic) AF (cAF). To elucidate the role of FKBP5 in cardiomyocytes (CMs), we established an inducible CM-specific FKBP5 knockdown (cKD) model ( $\alpha$ MHCMerCreMer:FKBP5<sup>fl/fl</sup>). At the age of 6 weeks, cKD mice were injected with tamoxifen (50mg/kg, 5 days, i.p.) to induce FKBP5 knockdown in CMs.

**Results:** Programmed electrical stimulation studies revealed that FKBP5-cKD mice were prone to pacing-induced AF than control mice (7.1% vs 52.4%,  $P < 0.05$ ), independent from ventricular dysfunction. Proteomics study revealed that FKBP5 interacted with several proteins involved in the membrane trafficking, such as SNX4 and EHD1, which was also confirmed by Co-IP and BiFC studies. we also found membrane located Na<sup>+</sup>/Ca<sup>2+</sup> exchanger 1 (NCX1) was increased by 50% cKD mice, compared to control mice ( $P < 0.05$ ). At last, we proved that SNX4 mediate the membrane trafficking of NCX1.

**Conclusions:** Our study establishes that FKBP5 deficiency promotes atrial arrhythmogenesis, likely via enhancing the membrane trafficking of NCX1, which could promote triggered activity. Future studies will elucidate the FKBP5-mediated ion channel trafficking.

**Poster Number 35**

**Clinical Fellow**

**Aortopathy**

**NINETY-DAY READMISSION AFTER OPEN SURGICAL REPAIR OF STANFORD TYPE A AORTIC DISSECTION**

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**Background:** Evaluation of readmissions after surgical repair of Stanford Type A aortic dissection (TAAD) remain scarce. We analyzed potential risk factors for readmission after TAAD.

**Materials/Methods:** The 2013-2014 Nationwide Readmissions Database was queried for TAAD index hospitalizations and 90-day readmissions through ICD-9 diagnostic and procedural codes. Multivariable analysis revealed risk factors for and common causes of readmission.

**Results:** Overall, 2,062 out of 6,975 (29.6%) patients were readmitted within 90 days following surgical repair of TAAD: 634 (30.7%) during day 1-30 versus 1,428 (69.3%) at the 31-90 day interval. Readmitted patients had a higher prevalence of chronic kidney disease (18.0% vs 11.6%,  $P < .01$ ) and greater hospitalization cost (\$90,637 $\pm$ \$2,691 vs \$80,082 $\pm$ \$2,091;  $P < .01$ ) during index admission. Multivariate analysis identified acute kidney injury (OR 1.49; 95% CI 1.24-1.78,  $P < .01$ ) and an Elixhauser Comorbidity Index  $>4$  (OR 1.26; 95% CI 1.06-1.49,  $P < .01$ ) as independent readmission risk factors. Cardiac (26.2%), infectious (17.8%), and pulmonary (11.7%) complications were the most common readmission etiologies; mortality during the readmission period was 3.6% ( $n = 74$ ).

**Conclusions:** Approximately 30% of TAAD surgical repair patients were readmitted within 90 days. Concentrated efforts in perioperative care and post-discharge follow-up of patients with multiple comorbidities should be continued during this window to help improve patient outcomes, mitigate readmission rates, and reduce hospital costs.

**Poster Number 36**

**Clinical Fellow**

**Aortopathy**

**BONE DENSITY SCREENING IN VASCULAR EHLERS-DANLOS SYNDROME**

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**Background:** Multiple connective tissue disorders are associated with low bone density. Preliminary studies examining bone density in Vascular Ehlers-Danlos syndrome (VEDS) have not focused on children and young adults. We aimed to describe bone density in this cohort.

**Materials/Methods:** We performed a retrospective review of records for patients <35 years old evaluated at our center and collected clinically performed studies. Bone density evaluation using dual energy x-ray absorptiometry (DEXA) became standard of care for baseline evaluation at our institution in 2019 for patients with VEDS. Z-scores were calculated for age, sex, and race-matched controls and compared against the expected population value of "0" using one-sample Wilcoxon signed-rank analysis.

**Results:** Eighteen patients underwent DEXA (median age at testing 9.5 years, range 5.0-33.4y; 89% male). Variant types were: 10 splice site, 6 glycine missense, 1 nonsense, and 1 multigene deletion. Four had a z-score <-2 for at least one region. The patient with a multigene deletion had z-scores far outside the expected range and was excluded from other analyses. Remaining median z-scores were <0, but did not meet statistical significance. When stratifying by genotype, similar patterns were noted.

**Conclusions:** Low bone density was observed more frequently in this cohort than seen in the general population. These findings may have long-term implications for therapeutic strategies. Integrating bone density evaluation into this population's clinical care should be considered.

**Poster Number 37**

**Clinical Fellow**

**Aortopathy**

# **AORTIC ROOT REPLACEMENT SURGERY IN PATIENTS WITH CORONARY ARTERY DISEASE**

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**Background:** The relationship between coronary artery disease (CAD) on patients who undergo aortic root replacement (ARR) is unclear.

**Materials/Methods:** We retrospectively reviewed data from 1000 consecutive patients who underwent ARR to compare patients with CAD (n=213) to those without (n=787). Multivariable modeling was performed to identify predictors of operative death.

**Results:** Patients with CAD were older (age 61 [55-68] vs 50 [38-60];  $p<.001$ ) and had more cerebrovascular (17% vs 9%;  $p=.001$ ), pulmonary (20% vs 12%;  $p=.003$ ), chronic kidney (21% vs 12%;  $p=.001$ ), and other disease than did those without CAD. Operative times were longer in those with CAD than in those without, namely times for aortic cross-clamp (106 [88-135] vs 97 [83-117];  $p=.003$ ), cardiopulmonary bypass (184 [157-224] vs 162 [139-197];  $p<.001$ ), and cardiac ischemia (124 [105-151] vs 113 [96-134];  $p<.001$ ). Operative mortality was significantly higher in ARR patients with CAD than in those without (15% [32/213] vs 7% [51/787]  $p<.001$ ) as was persistent renal failure necessitating dialysis (9% [19/213] vs 3% [23/787]  $p<.001$ ). Multivariable modeling did not identify CAD as a predictor of operative death. Kaplan Meier survival analysis showed CAD ARR patients had worse survival over a 10-year period (45% vs 70% at 10-years;  $p<.001$ ).

**Conclusions:** Patients with CAD undergoing ARR are older, have diminished health, face complex repair, and have worse outcomes than those without CAD. Strategies targeted to patients with CAD are needed.



## Poster Number 38

### Student

### Aortopathy

#### **A 23-YEAR EXPERIENCE WITH THE REVERSED ELEPHANT TRUNK TECHNIQUE FOR STAGED REPAIR OF EXTENSIVE THORACIC AORTIC ANEURYSM**

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<sup>1</sup> Surgery, Baylor College of Medicine, Houston, TX

**Background:** The reversed elephant trunk technique permits staged repair of extensive thoracic aortic aneurysm in patients whose distal aorta is symptomatic or disproportionately large compared with their proximal aorta.

**Materials/Methods:** Between 1994 and 2017, 94 patients underwent stage 1 reversed elephant trunk repair of the distal aorta. Fifty-three patients (56%) had aortic dissection, and 31 patients (33%) had heritable thoracic aortic disease. Eighty-eight operations (94%) were Crawford extent I or II thoracoabdominal aortic repairs. Twenty-seven patients (29%) underwent subsequent stage 2 repair of the proximal aorta. The median time between the stage 1 and 2 operations was 18.8 (4.8-69.3) months.

**Results:** The operative mortality was 10% (9/94) for stage 1 repairs and 4% (1/27) for stage 2 repairs; 1 patient with heritable thoracic aortic disease died after stage 1 repair (1/31, 3%), and 1 patient died after stage 2 repair (1/13, 8%). Two patients (2%) had ruptures after stage 1 repair; 1 resulted in death, and 1 precipitated emergency stage 2 repair. In total, 36 patients (38%) who survived stage 1 repair died before stage 2 reversed elephant trunk completion repair could be performed.

**Conclusions:** Managing extensive aortic aneurysm with the 2-stage reversed elephant trunk technique yields acceptable short-term outcomes. This technique is particularly effective in patients with heritable thoracic aortic disease. The low number of patients returning for completion repair is concerning. Rigorous surveillance is needed.

**Poster Number 39**

**Junior Faculty**

**Aortopathy**

**HIGH FIDELITY COMPUTER MODELS FOR CARDIAC FLUID AND SOLID MECHANICS**

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**Background:** The goal of this work is to construct physics-based models of the entire human heart, including the blood, valves, heart chambers, and the surrounding great vessels. Our models are constructed from clinical imaging data and incorporate realistic anisotropic descriptions for each component. We also include descriptions of the preload and afterload on the heart. Our hypothesis is that these models will be very useful for virtually studying interventions in congenital heart disease, including experimental medical devices and surgical procedures.

**Materials/Methods:** Model geometries are generated from MRA and CT imaging data. These geometries are included in a numerical framework called the immersed boundary method. In this approach, equations for blood flow are coupled to hyperelastic solid mechanics models for the heart tissue, valves, and great vessels. The equations are solved numerically to predict the blood velocity field as well as the displacements for all of the model components.

**Results:** We are currently working on calibrating our models to normal physiological conditions. It is able to produce a cardiac cycle with close-to physiological pressures and flows.

**Conclusions:** This work describes an approach for developing some of the most detailed physics-based models of cardiac mechanics available. These models will be applied to virtually simulate experimental procedures that would otherwise be challenging to study using only clinical experience.

## Poster Number 40

### Clinical Fellow

### Aortopathy

#### MACHINE LEARNING TO PREDICT OUTCOMES AND COST AFTER CARDIAC SURGERY

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**Background:** Machine learning (ML) may enhance surgical outcome prediction and help guide clinical decision making. In cardiac surgery, risk prognostication with traditional statistical methods remains limited to specific operations and few models exist to predict cost.

**Materials/Methods:** The Baylor College of Medicine Society of Thoracic Surgery Adult Cardiac Surgery database from 2015-2019 was queried for all patients (n=4,065) who underwent cardiac surgery. Predictors included preoperative clinical and laboratory data. Outcomes were 30-day mortality and high (>75th percentile; >\$59,216) cost. A decision tree ML model was created with 84 input parameters, then refined to a final model. The final model performance was assessed using accuracy and area under the receiver operator characteristic curve (AUC).

**Results:** For 30-day mortality, the final model identified 15 preoperative parameters providing similar accuracy to 84 parameters. The most predictive parameters included weight, height, platelets, leukocyte count, creatinine and ejection fraction. Accuracy was 97%, with an AUC of 0.83. For high cost, the most predictive included hemoglobin, platelets, creatinine, weight, and ejection fraction. Accuracy was 83%, with an AUC of 0.80.

**Conclusions:** Using a decision tree ML model, 30-day mortality and high cost after cardiac surgery can be predicted with an accuracy of 97% and 80%, respectively. Markers of heart failure, weight, and common laboratory results have the highest impact in outcome predictions.

## Poster Number 41

### Clinical Fellow

### Aortopathy

## ACUTE DEBAKEY TYPE II DISSECTION MIMICS LEFT VENTRICLE OUTFLOW TRACT OBSTRUCTION

Davut Cekmecelioglu<sup>1</sup>, Vicente Orozco-Sevilla<sup>1</sup>, Ourania Preventza<sup>1</sup>, Subhasis Chatterjee<sup>1</sup>, Joseph Coselli<sup>1</sup>

<sup>1</sup>Cardiothoracic Surgery, Baylor College of Medicine, Houston, TX

**Background:** A 40-year-old man with hypertension and obesity (body mass index, 50.4 kg/m<sup>2</sup> ) was referred to our institution after an evaluation for symptoms of heart failure (worsening shortness of breath for 2 weeks).

**Materials/Methods:** Computed tomography with contrast revealed subacute DeBakey type II aortic dissection originating at the sinotubular junction with an enlarged thrombus occupying the false lumen and obstructing blood flow through the stenotic supra-ventricular aorta.

**Results:** During emergency surgical repair, intraoperative transesophageal echocardiography was performed. Long-axis views (with and without color Doppler) showed a normal aortic root, thickened tricuspid leaflets, and mild aortic valve regurgitation. Thrombus within the false lumen induced a trans-aortic jet of 3.4 m/s peak velocity at the level of the sinotubular junction. Color Doppler confirmed severe mitral regurgitation, which was addressed with ring annuloplasty. The dissection flap and thrombus were confirmed intraoperatively.

**Conclusions:** Supra-ventricular aortic stenosis is usually a congenital obstructive narrowing of the aorta and is the rarest lesion on the left ventricular outflow tract obstruction spectrum. Dissection of the ascending aorta with extensive thrombosis of the false lumen obstructing the left ventricular outflow tract is an extremely uncommon presentation that can mimic the negative hemodynamic effects of the congenital forms and should be considered in the differential diagnosis of aortic dissection with atypical presentations.

## Poster Number 42

### Student

### Arrhythmia

## MULTIPLEX GENOME EDITING FOR THE TREATMENT OF CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Charles T Moore<sup>1</sup>, Oliver Moore<sup>1</sup>, Jayso'n Davidson<sup>1</sup>, Juwan Copeland<sup>1</sup>, William Lagor<sup>1</sup>, Xander Wehrens<sup>1</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX

**Background:** Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited sudden cardiac death syndrome induced by stress or exercise that can affect children and young adults. Mutations in the ryanodine receptor type two (RYR2) cause CPVT by increasing diastolic calcium leak that can trigger lethal arrhythmias. Previously our lab showed that allele specific editing of the RyR2-R176Q mutation was sufficient to prevent inducible ventricular tachycardia. Our objective is to design vectors that can treat more than one mutation causative of CPVT. Our hypothesis is that allele specific editing of multiple mutations for CPVT will have similar efficacies to sgRNA and minimal off target effects on wild type allele. Furthermore, we predict that over-expression of mutant RyR2 binding partner FKBP12.6 may stabilize the channel to prevent diastolic calcium independent of mutation.

**Materials/Methods:** We designed single guide RNAs (sgRNA) to target the N-terminal RQ and central domain RyR2-R2474S (RS) mutation sites. We cloned vectors with sgRNA targeting RS or RQ, dual guides targeting RS + RQ, and no gRNA as control. We used an in-vitro luciferase assay to determine on and off target editing efficiencies. We generated AAV9 with CRISPR/Cas9 and injected SC p5 mice. We generated AAV9 overexpressing FKBP12.6 D37V and injected SC p5 mice. 6 weeks after injection, mice underwent ECG stress testing with isoproterenol, caffeine, and programmed electrical stimulation.

**Results:** We found by targeting the RQ site with sgRNA/Cas9, 0/8 mice had pacing-induced VT compared to 6/8 control ( $p=0.03$ ). When targeting the RS site with sgRNA/Cas9, 0/7 mice had inducible VT compared to 6/7 control ( $p=0.04$ ). The luciferase assay showed similar editing efficiencies with sgRNA and dual gRNA ( $\Delta <10\%$ ) with preserved specificity to mutant alleles ( $>80\%$ ). In ongoing experiments, we expect similar efficacies in CPVT mice treated with dual gRNA/Cas9. Mice treated with mutant FKBP12.6 overexpression had 0/3 inducible VT compared to 0/4 control.

**Conclusions:** CRISPR/Cas9 gene editing can treat CPVT by specifically disrupting causative mutation sites in multiple channel domains. Over expression of mutant FKBP12.6 may be able to treat multiple mutations causative of CPVT by stabilizing the RyR2 receptor. Through successful treatment of multiple models of CPVT, we have promising preclinical data for gene therapy as a potential treatments for CPVT.

## Poster Number 43

### Student

### Arrhythmia

## LONG-TERM EVALUATION OF AAV-CRISPR GENOME EDITING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Oliver M Moore<sup>1</sup>, Jayso'n Davidson<sup>1</sup>, Tarah Word<sup>1</sup>, Hannah Campbell<sup>1</sup>, William Lagor<sup>1</sup>, Xander Wehrens<sup>1</sup>

<sup>1</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX

**Background:** Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia disorder that can cause sudden cardiac death. Variants in the ryanodine receptor type 2 gene (RYR2) cause >60% of CPVT cases. These variants increase RyR2 calcium (Ca<sup>2+</sup>) leak from the sarcoplasmic reticulum that can trigger ventricular arrhythmias. Current therapeutic options are partially effective. Previously, our lab showed that using the CRISPR/Cas9 genome editing system targeting a silent restriction site could disrupt a disease-causing allele preventing VT in a CPVT mouse model with RyR2-R176Q mutation. Our objective is to evaluate the long term efficacy and safety of AAV-CRISPR genome editing for CPVT. We hypothesize that allele specific editing of mutant RyR2 will treat CPVT with minimal long term deleterious effects on baseline cardiac function.

**Materials/Methods:** We designed single guide RNAs (sgRNA) to target the N-terminal R176Q mutation site. We cloned vectors with sgRNA targeting the R176Q mutation or without sgRNA as control. We generated AAV9 with CRISPR/Cas9 and injected SC p5 mice. 6 weeks after injection, mice underwent ECG stress testing with isoproterenol, caffeine, and programmed electrical stimulation. Isolated ventricular cardiomyocytes loaded with Fluo4 dye were analyzed with confocal line scanning. Mice were followed with serial electrocardiogram and echocardiography every 3 months for 12 months.

**Results:** We found by targeting the RQ site with sgRNA/Cas9, 0/8 mice had pacing-induced VT compared to 6/8 control (p=0.03). Edited cardiomyocytes showed a significant reduction in Ca<sup>2+</sup> spark frequency (p<0.01). Echocardiography showed no significant change in ejection fraction or pulmonary artery velocity. Electrocardiograms showed no significant changes in baseline heart rate or electrocardiogram parameters.

**Conclusions:** CRISPR/Cas9 gene editing can treat CPVT by specifically targeting causative mutation sites, reducing mutant allele expression and preventing Ca<sup>2+</sup> leak in the long term without deleterious effects on systolic or diastolic cardiac function. Through successful targeting of the mutation sites, we have promising preclinical data for gene editing as a permanent cure for CPVT.

## Poster Number 44

### Student

### Arrhythmia

## IN SILICO VALIDATION OF GENOME EDITING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Vaidya Parthasarathy<sup>1</sup>, Oliver Moore<sup>2</sup>, William Lagor<sup>2</sup>, Xander H Wehrens<sup>2</sup>

<sup>1</sup>Physiology, Rice University; <sup>2</sup>Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX

**Background:** Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia that is most infamous for causing sudden death in children and adults. CPVT is estimated to have a prevalence of 1 in 10,000 people. This disorder is characterized by an abnormal release of Ca<sup>2+</sup> from the sarcoplasmic reticulum (SR) during the relaxation of beating heart cells (cardiomyocytes). This leads to delayed afterdepolarizations that can trigger arrhythmias when an individual exercises or experience stress. CRISPR-Cas9 genome editing is a method that has been proposed to correct CPVT since usually only one mutated allele causes presentation of the disease. However, there are more than 140 known mutations of CPVT. In order to streamline and optimize CPVT genetic editing research, we hypothesize that in silico algorithms can accurately survey all the CPVT causing mutations on the RyR2 gene by guide cut-site region, on target effects, and off target effects

**Materials/Methods:** Literature was searched for mutations pertaining to CPVT. 100 base pair fragments were created, centered around all the found mutation sites. Then using the benchling.com's algorithm for calculation of on target scores of saCas9 (pam site: NNGRRT) guides and spCas9 (pam site: NGG) guides, the highest possible on target score for editing the specific mutation site was determined.

**Results:** We tested spCas9 guide's ability to target the region which includes the mutation site from the on target analysis method. 84.17% of SpCas9 guides meet the required 25 on target score threshold. We also tested SaCas9 guide's ability to target the region which guide's ability to target the region. We found that 11.51% of SaCas9 guides meet the required 25 on target score threshold.

**Conclusions:** We have found that more than 80% of CPVT causing variants are targetable with common Cas9 orthologs. This project shows a method of analysis that will help to streamline the process of genome editing mutations for CPVT. This project can easily be expanded to include analysis of other genome editing strategies including base editing.

## Poster Number 45

### Clinical Fellow

### Arrhythmia

#### **A NOVEL MANNOSE RECEPTOR C-TYPE 2 VARIANT IDENTIFIED IN INDIVIDUALS WITH FAMILIAL WOLFF-PARKINSON-WHITE SYNDROME**

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**Background:** Wolff-Parkinson-White (WPW) syndrome is the most common arrhythmia disorder observed in patients with structurally normal hearts and can lead to supraventricular tachycardia (SVT) and sudden cardiac death. The genetic basis of WPW syndrome in individuals with structurally normal hearts remains unknown.

**Materials/Methods:** Whole exome sequencing (WES) was performed on two members of a three-generation extended family in which multiple members were affected by SVT, WPW pattern, or WPW syndrome. Shared non-synonymous variants were then tested in all other family, as well as unrelated individuals with WPW syndrome. An Mrc2 E990G knock-in mouse model was generated and subjected to resting ECGs, programmed electrical stimulation (PES), echocardiography and optical mapping.

**Results:** WES revealed a novel monogenic heterozygous variant E990G in Mannose Receptor C-Type 2 (Mrc2). WPW pattern was not present on baseline ECGs in E990G knock-in mice, but a significantly higher incidence of inducible SVT following PES was observed. Furthermore, optical mapping studies demonstrated the presence of a re-entry bypass tract. Echocardiography showed preserved cardiac structure or function in E990G mice.

**Conclusions:** This study identifies a novel non-synonymous variant E990G in the gene Mrc2 in familial WPW syndrome. Furthermore, the presence of this variant in a murine model leads to increased incidence of SVT and bypass tract formation in the setting of preserved cardiac structure and function.



## Poster Number 46

### Clinical Fellow

### Arrhythmia

#### THE PROGNOSTIC ROLE OF MATRIX METALLOPROTEINASE 7 (MMP-7) IN AN ELDERLY AND BIRACIAL POPULATION: ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

Ali M Agha<sup>1</sup>, Aliza Hussain<sup>2</sup>, Amil M Shah<sup>3</sup>, Ron Hoogeveen<sup>4</sup>, Wensheng Sun<sup>4</sup>, Salim S Virani<sup>2</sup>, Vijay Nambi<sup>4</sup>, Bing Yu<sup>5</sup>, Elizabeth Selvin<sup>6</sup>, Kunihiro Matsushita<sup>6</sup>, Leo Buckley<sup>7</sup>, Lin Chen<sup>8</sup>, Pranav Dorbala<sup>9</sup>, Christie M Ballantyne<sup>4</sup>

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**Background:** We sought to determine if matrix metalloproteinase 7 (MMP-7) was associated with cardiac structure/function and CV events in an elderly biracial population-based study.

**Materials/Methods:** MMP-7 was measured using the aptamer based SOMALogic assay among 5,281 participants at visit 5 of the Atherosclerosis Risk in Communities (ARIC) study (2011-2103), mean age 75.8 (SD 5.24), 43.2% men, and 18.7% black. We used linear regression to assess the cross-sectional association of MMP-7 with echocardiographic parameters. We used Cox regression to evaluate associations of these biomarkers with heart failure hospitalizations (HFH), atherosclerotic cardiovascular disease (ASCVD) events, and death over approximately 6-year follow-up with adjustment for risk factors.

**Results:** In models adjusted for traditional risk factors, CKD, and hs-CRP, MMP-7 showed a cross-sectional association with echocardiographic parameters including positive correlations with LVMI ( $p<0.001$ ), LAVi ( $p=0.004$ ), septal  $e'$  ( $p=0.004$ ), and septal  $E/e'$  ( $p=0.006$ ). Increased MMP-7 levels were associated with incident ASCVD events ( $p=0.005$ ), HFH ( $p<0.001$ ), global CVD events ( $p<0.001$ ), CV-death ( $p<0.001$ ), and non-CV death ( $p<0.001$ ).

**Conclusions:** In an elderly biracial population-based study, increased levels of MMP-7 were associated with echocardiographic parameters related to hypertrophy and diastolic dysfunction in addition to increased risk for incident ASCVD events, heart failure hospitalizations, and both CV and non-CV death.

**Poster Number 47**

**Student**

**Arrhythmia**

**RESPIRATORY FAILURE REQUIRING TRACHEOSTOMY IN LVAD PATIENTS: A PROPENSITY MATCHED ANALYSIS**

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**Background:** Respiratory failure requiring tracheostomy after left ventricular assist device (LVAD) implantation is a major postoperative development. The purpose of this study was to investigate outcomes after tracheostomy in patients undergoing LVAD implantation. We hypothesized that tracheostomy patients would be at increased risk of adverse outcomes.

**Materials/Methods:** Retrospective review of 665 patients who underwent LVAD implantation at our institution. Post-operative respiratory failure requiring tracheostomy occurred in 105 (15.8%). Risk factors for tracheostomy were evaluated. After propensity score matching, 104 pairs of tracheostomy and non-tracheostomy patients were compared for mortality and adverse events.

**Results:** In the unmatched cohort, patients requiring tracheostomy were older, implanted more often for destination therapy, had more preoperative mechanical circulatory support, and more prior sternotomies. After matching, the two groups were comparable for these risk factors. During a mean follow-up of  $1.5 \pm 2.0$  years, the mortality in the tracheostomy group (76.0%, n=79) was higher than the non-tracheostomy group (46.2%, n=48;  $p < 0.001$ ). The risk of postoperative renal failure and reoperation for bleeding were also associated with tracheostomy.

**Conclusions:** Tracheostomy was found to be an independent predictor of decreased survival after LVAD implantation. These data emphasize the need for appropriate patient selection and optimal management to reduce the incidence of tracheostomy after LVAD implantation.

**Poster Number 48**

**Clinical Fellow**

**Arrhythmia**

**ADIPONECTIN AND CARDIOVASCULAR DISEASE IN OLDER ADULTS – INSIGHTS FROM THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY**

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<sup>1</sup>Medicine-Cardiology, Baylor College of Medicine, Houston, TX

**Background:** Among individuals who have survived to older age without clinical cardiovascular disease (CVD), processes that portend to future CVD events may extend beyond traditional cardiac risk factors. We investigate the association of specific adiponectin phenotypes and cardiovascular disease (CVD) risk in older adults.

**Materials/Methods:** Atherosclerosis Risk in Communities study participants at older age without baseline CVD were included in primary analysis (n=4729). Cox proportional hazard models were used to assess association between adiponectin with incident heart failure (HF) hospitalization, coronary heart disease (CHD), ischemic stroke, and CVD death. Association between categories by adiponectin and NT-proBNP with outcome events was also evaluated.

**Results:** In older adults without baseline CVD, higher adiponectin was associated with increased risk for incident HF events (HR 1.91, 95% CI 1.49-2.44, p<0.001 per natural-log unit increase in adiponectin) and CVD death (HR 1.67, 95% CI 1.19-2.32, p=0.003) but not CHD or stroke despite association with a more favorable cardiometabolic profile. Compared with individuals with elevated adiponectin without elevated NT-proBNP, those with elevated NT-proBNP alone and concurrent elevation of both biomarkers were associated with incrementally increasing risk for HF and CVD deaths.

**Conclusions:** Concurrently elevated adiponectin and NT-proBNP represents a unique phenotype in older adults with increased risk for HF and death independent of traditional cardiometabolic risk factors.

**Poster Number 49**

**Postdoctoral Researcher**

**Coronary Artery Disease**

**A PRACTICAL SOLUTION BASED ON DAILY USE OF LOWER LIMB ELECTRICAL STIMULATION THERAPY TO PREVENT ICU ACQUIRED WEAKNESS IN CRITICAL ILL ICU PATIENTS WITH SEVERE COVID-9 INFECTION – A PROOF OF CONCEPT DOUBLE BLINDED RANDOMIZED CONTROL TRIAL**

Alejandro Zulbaran<sup>1</sup>, Ramkinker Mishra<sup>1</sup>, Naima Rodriguez<sup>1</sup>, James P Herlihy<sup>2</sup>, Muhammad Siddique<sup>2</sup>, Bijan Najafi<sup>1</sup>

<sup>1</sup>Vascular Surgery and Endovascular Therapy, Baylor College of Medicine, Houston, TX; <sup>2</sup>Pulmonary Critical Care, Baylor College of Medicine

**Background:** Prolonged bed rest and use of glucocorticoids/paralytics may lead to lower limb myopathy among COVID-19 ICU patients. Electrical stimulation (E-Stim) has shown to preserve muscle strength and mass, which may offer a unique treatment for this patient population. This randomized control trial examined the feasibility and proof of concept effectiveness of E-Stim to prevent ICU acquired weakness.

**Materials/Methods:** 12 patients with severe COVID-19 admitted to the ICU were recruited and randomized to either control (CG: n=6) or intervention (IG: n=6) groups. The IG received 1-hour E-Stim on both gastrocnemius muscles (GNM) using a bio-electric stimulation technology platform on daily-basis during the ICU stay. The CG was provided an identical non-functional device. Surface electromyography on GNM was used to evaluate fatigue in response to E-Stim with further maximum voluntary contraction (MVC), and circumference (CF) assessments recorded at baseline (BL), and further weekly or discharge date from ICU (EP). Plantar tissue oxygen saturation (SatO2) was assessed with near infrared spectroscopy.

**Results:** No muscle fatigue was observed in IG in response to E-stim. At EP, a non-significant trend with medium to large effect sizes (Cohen's d=0.48-1.37) for all metrics in response to E-Stim was observed.

**Conclusions:** This initial observation support the potential benefit of lower limb E-Stim to improve perfusion and prevent ICU acquired weakness in patients with COVID-19. A larger population is warrant to confirm this statement

**Poster Number 50**

**Postdoctoral Researcher**

**Coronary Artery Disease**

**EFFECTIVENESS OF ELECTRICAL STIMULATION TO IMPROVE LOWER EXTREMITY MUSCLE PERFUSION IN CRITICAL ILL ICU PATIENTS WITH SEVERE COVID-19 INFECTION**

Alejandro Zulbaran<sup>1</sup>, Ramkinker Mishra<sup>1</sup>, Naima Rodriguez<sup>1</sup>, James P Herlihy<sup>2</sup>, Muhammad Siddique<sup>2</sup>, Bijan Najafi<sup>1</sup>

<sup>1</sup>Vascular Surgery and Endovascular Therapy, Baylor College of Medicine, Houston, TX; <sup>2</sup>Pulmonary Critical Care, Baylor College of Medicine

**Background:** Critically ill ICU patients often suffer from pronounced loss of lower extremity muscle mass and perfusion due to prolonged bed rest. This condition is highly prevalent among severe COVID-19 patients due to respiratory failure and low arterial saturation of oxygen. We examined the effectiveness of lower extremity electrical stimulation (E-Stim) to improve muscle perfusion and activation in this population.

**Materials/Methods:** Twelve patients with respiratory failure due to severe COVID-19 infection admitted to the ICU were recruited. Participants underwent 60-minutes of active E-Stim provided on both gastrocnemius muscles using a bio-electric stimulation technology platform. Surface electromyogram was recorded to assess changes in muscle activation (root mean square [RMS]) and fatigue (mean frequency [MNF]). Near infrared spectroscopy was used to assess changes in plantar tissue oxygen saturation (SatO<sub>2</sub>). Parameters were measured at baseline (BL), and 60-min of E-stim therapy.

**Results:** SatO<sub>2</sub> increased in response to E-Stim at 60-min from BL (4%,  $p=0.02$ ,  $d=0.525$ ). No changes in RMS ( $p=0.19$ ,  $d=0.41$ ) and MNF ( $p=0.86$ ,  $d=0.03$ ) were observed. There was a significant correlation between SatO<sub>2</sub> and RMS through time ( $d=0.675$ ,  $p=0.016$ ).

**Conclusions:** Increase in lower limb perfusion after one hour of E-stim and concurrent increase in RMS level shows potential benefit for muscle preservation in this population. No significant change in MNF reflects that patients were able to undergo E-Stim without muscle fatigue.

**Poster Number 51**

**Clinical Fellow**

**Coronary Artery Disease**

**ULTRASOUND ACCELERATION FAILS TO SHOW SUPERIORITY OVER STANDARD CATHETER-DIRECTED THROMBOLYSIS FOR KEY RADIOGRAPHIC PARAMETERS OF RIGHT HEART STRAIN IN ACUTE PULMONARY EMBOLISM: AN INTERIM META-ANALYSIS**

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**Background:** Compared with systemic thrombolysis for acute pulmonary embolism (PE), catheter-directed thrombolysis (CDT) reduces bleeding risk due to lower thrombolytic doses, while maintaining efficacy. The only FDA-approved device for CDT is a more expensive ultrasound-accelerated-CDT (USAT) device. No trials comparing CDT vs USAT exist

**Materials/Methods:** We performed a retrospective non-time-limited literature search using PubMed for all studies reporting outcomes of CDT or USAT. Meta-analyses were performed using RevMan 5.3 (Cochrane Collaboration). Effect sizes were calculated using mean difference (MD) and Chi2 with 95% confidence intervals, using Random Effects Model

**Results:** 17 USAT and 2 CDT studies evaluated change in RV/LV ratio (MD 0.35 [0.28-0.41] and 0.59 [0.47-0.70], Chi2=12.59, P=0.0004, I2=94%). 16 USAT and 2 CDT studies evaluated change in pulmonary artery systolic pressure (PASP) (MD 16.3 [15.16, 17.45] and 15.58 [11.00, 20.16], Chi2=0.09, P=0.76, I2=81%)

**Conclusions:** Our data show greater improvement in RV/LV, but not PASP, with standard CDT. However, very few studies report outcomes for standard CDT, and between-study heterogeneity is high. The sparse data represented here are likely underpowered to detect true difference. A more detailed meta-analysis including all studies which specify whether their data comes from CDT vs USAT, and which stratifies results by massive and submassive PE, is underway to provide interim answers while science awaits the results of the ongoing randomized-controlled clinical trial.

**Poster Number 52**

**Clinical Fellow**

**Coronary Artery Disease**

**FASTING BLOOD GLUCOSE (FBG) AND CARDIOVASCULAR DISEASE (CVD) RISK IN HISPANIC YOUTH WITH OBESITY**

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**Background:** Youth of minority race-ethnicity have higher prevalence of obesity and are at increase in risk for comorbidities. The relationship of FBG to CVD risk in youth is not clear. We investigated the relationship between FBG and CVD risk factors in a cohort of Hispanic youth with overweight (OW) and obesity (OB).

**Materials/Methods:** 372 (186 males) pubertal, non-diabetic adolescents; mean age (SD) 13.9±2.5 years; 26% OW and 74% OB underwent measurement of anthropometrics, blood pressure (BP); body composition; fasting glucose, insulin, CRP, ALT, AST, triglycerides (TG), total, LDL and HDL-cholesterol. The homeostasis model assessment of insulin resistance (HOMA-IR) and TG to HDL ratio were calculated. Subjects were divided into tertiles of FBG (<90 mg/dL, 90-96 mg/dL, >96 mg/dL) and compared using general linear model adjusting for sex.

**Results:** The three FBG tertiles didn't differ with respect to age, Tanner stage, %body fat, truncal fat, or liver transaminases. Measures of insulin resistance (IR), inflammation, dyslipidemia and BP including HOMA-IR ( $5.7 \pm 3.4$ ,  $7.2 \pm 4.4$ ,  $10.5 \pm 6.9$ ,  $p < .001$ ), TG/HDL ratio ( $2.8 \pm 1.3$ ,  $3.4 \pm 1.7$ ,  $3.5 \pm 1.9$ ,  $p = 0.003$ ) and systolic BP ( $112.2 \pm 9.1$ ,  $114.1 \pm 9.1$ ,  $116.8 \pm 10.1$  mmHg,  $p < .001$ ) increased across tertiles of FBG.

**Conclusions:** Elevated FBG in the non-diabetic range is associated with greater degree of IR, inflammation and adverse CVD risk profile, independent of total body or truncal fat. This data suggest that higher FBG identifies obese Hispanic youth at high risk for CVD.

**Poster Number 53**

**Student**

**Coronary Artery Disease**

**ROLE OF SMOOTH MUSCLE CELL METABOLIC ALTERATIONS IN PEDIATRIC ONSET STROKE**

Anita Kaw<sup>1</sup>, Abhijnan Chattopadhyay<sup>2</sup>, Callie Kwartler<sup>2</sup>, Dianna Milewicz<sup>2</sup>

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**Background:** Moyamoya disease (MMD) causes ischemic strokes in children characterized by smooth muscle cell (SMC)-staining occlusive lesions in the cerebral arteries. ACTA2 R179 mutations predispose to thoracic aortic aneurysms and dissections and MMD-like disease. ACTA2 encodes SMC-specific  $\alpha$ -actin which contributes to SMC contraction. We hypothesize that decreased aortic SMC contraction drives thoracic aortic disease, while increased proliferation and migration of SMCs cause occlusive disease in the cerebral arteries. Increasing oxidative phosphorylation (OXPHOS) is necessary and sufficient to differentiate stem cells and promote quiescence in tumors.

**Materials/Methods:** We generated an SMC-specific Acta2 SMC-R179C/+ mouse model via the Cre-Lox system. Phenotypic differences between mutant and WT brains are characterized using micro CT and echocardiography. SMC phenotype is evaluated by expression of contractile genes, proliferation, migration, and immunofluorescence. Metabolic differences are assessed with Seahorse assays.

**Results:** Patient-derived ACTA2 R179C SMCs and explanted SMCs from Acta2 SMC-R179C/+ mice exhibit decreased differentiation and increased proliferation and migration. Acta2 SMC-R179C/+ SMCs also have increased glycolysis and decreased OXPHOS. Nicotinamide riboside (NR) drives Acta2 SMC-R179C/+ SMC differentiation and decreases migration. Mutant mice display straightened cerebral arteries but no aortic disease.

**Conclusions:** Using NR to boost OXPHOS drives differentiation and decreases migration in mutant SMCs.



**Poster Number 54**

**Postdoctoral Researcher**

**Coronary Artery Disease**

## **EFFECTIVENESS OF LOWER EXTREMITY ELECTRICAL STIMULATION TO IMPROVE SKIN PERFUSION**

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**Background:** This study examined the potential effectiveness of lower extremity E-Stim therapy to improve tissue perfusion in patients with diabetic foot ulcers (DFUs).

**Materials/Methods:** Patients with DFUs (n=38, 62.8±12.3 yrs, wound area: 4.6±7 cm<sup>2</sup>) underwent 60-minutes of electrical stimulation (E-Stim) therapy provided at ankle joint using a bio-electric stimulation technology (BESTTM). Changes in perfusion in response to E-Stim therapy were assessed by measuring skin perfusion pressure (SPP) at baseline, 30-, 60-, and 10-minutes post-therapy (retention). A subgroup of patients with moderate-severe peripheral arterial disease (ankle brachial index of < 0.8 or >1.4) was assessed with a near-infrared camera to detect tissue oxygen saturation (SatO<sub>2</sub>).

**Results:** SPP increased over time (p=0.02), and its maximum level was observed after 60-min (11% higher, p=0.007) compared to baseline. Subgroup showed a baseline SatO<sub>2</sub> below 75% which increased after 30-min (13.1% higher) and 60-min (12.9% higher) compared to baseline (all p<0.05). SatO<sub>2</sub> was also increased at 60-min compared to retention (p=0.003). Improvements at 60-min were correlated with baseline SPP (r=-0.45, p=0.01) and SatO<sub>2</sub> (subgroup) (r=-0.79, p<0.001).

**Conclusions:** This study shows the feasibility and effectiveness of E-Stim therapy to improve skin perfusion and address lower foot perfusion in patients with DFUs. Results suggest that E-Stim's effects could be washed out after stopping therapy, and regular daily application may be required for the benefit of wound healing.

**Poster Number 55**

**Postdoctoral Researcher**

**Coronary Artery Disease**

**EFFECTIVENESS OF DAILY HOME ELECTRICAL STIMULATION AS AN ADJUNCTIVE THERAPY TO ACCELERATE WOUND HEALING IN PEOPLE WITH DIABETIC FOOT ULCER – A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL**

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**Background:** Electrical stimulation (E-Stim) may offer a unique adjunctive treatment to heal complicated diabetic foot ulcers (DFU). Our primary goal is to examine the effectiveness of daily home-based E-Stim therapy to speed-up wound healing.

**Materials/Methods:** Patients with chronic DFUs and mild to severe peripheral arterial disease (PAD) were recruited and randomized to either control (CG) or intervention (IG) groups. The IG received 1-hour home-based E-Stim therapy on daily basis for 4 weeks (4W). E-stim was delivered through electrical pads placed above the ankle joint using a bio-electric stimulation technology® platform (Tennant Biomodulator® PRO). The CG was provided with an identical but non-functional device for the same period. The primary outcome included wound area reduction at 4W from baseline (BL).

**Results:** Thirty-eight patients with additional comorbidities (BMI=30.85kg/m<sup>2</sup>, chronic kidney disease=40%, hyperlipidemia=40%, coronary artery disease=30.3%, congestive heart failure=21%) were recruited and five were removed due to non-compliance or infection, leaving thirty-three participants (IG, n=16; CG, n=17). At 4W, IG showed a significant wound area reduction of 35% (BL: 7.4 ± 8.5 cm<sup>2</sup> vs 4W: 5.8 ± 8.0 cm<sup>2</sup>, p=0.002). Average of wound area was unchanged in CG (p=0.982). The self-report adherence to daily home-therapy was 93.9%.

**Conclusions:** This study provides early results on the feasibility, acceptability, and effectiveness of E-stim as an adjunctive therapy to speed up wound healing in people with chronic DFUs.

**Poster Number 56**

**Postdoctoral Researcher**

**Aortopathy**

**EFFECT OF NANOPARTICLE SIZE ON DETECTION OF AORTIC DEGENERATION USING NANOPARTICLE CONTRAST-ENHANCED COMPUTED TOMOGRAPHY IMAGING**

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**Background:** Early detection and prediction of disease progression are critical for improving outcomes in patients with aortic aneurysms and dissections (AAD). In a recent preclinical study, we demonstrated that contrast-enhanced computed tomography using a nanoparticle contrast agent (n-CECT) could enable early detection of aortic wall injury and inflammation before vessel enlargement is evident on CT angiography. In this work, we investigated if nanoparticle size impacts the sensitivity for early detection of aortic degeneration that leads to AAD. Additionally, we performed a longitudinal study to examine the long-term intramural fate of nanoparticle contrast agent (NPCA).

**Materials/Methods:** In a mouse model of sporadic AAD, 4 week-old C57BL/6J mice (n=8; 4M+4F) were challenged with high fat diet (HFD) for 5 weeks and subcutaneous angiotensin-II (Ang II; 2000 ng/min/kg) infusion during the last week. Animals were intravenously administered with one of three NPCA size variants (80, 150 and 250 nm; dose:1200 mg I/kg) at one day after start of Ang II infusion. Animals underwent in vivo CT delayed (CTD) imaging at 4 days post-contrast. A subset of animals underwent longitudinal imaging for up to 6 months to monitor long-term fate of NPCAs that accumulated at sites of aortic pathology. Ex vivo n-CECT imaging and gross examination were performed on excised aortas for comparison with in vivo CTD imaging.

**Results:** All NPCA size variants showed a higher incidence of n-CECT imaging findings compared to gross examination. Ex vivo n-CECT findings and gross examination findings were present in 79% and 67% for 80 nm, 52% and 24% for 150 nm, and 54% and 46% for 250 nm respectively. Longitudinal imaging demonstrated clearance of a majority of intramural NPCA by the end of six-month monitoring period.

**Conclusions:** Regardless of NPCA size, n-CECT imaging showed higher sensitivity for early detection of aortic degeneration compared to gross examination.

**Poster Number 57**

**Student**

**Aortopathy**

**EARLY GASTROINTESTINAL COMPLICATIONS AFTER OPEN THORACOABDOMINAL AORTIC ANEURYSM REPAIR**

William C Frankel<sup>1</sup>, Susan Y Green<sup>1</sup>, Hiruni S Amarasekara<sup>1</sup>, Qianzi Zhang<sup>2</sup>, Ourania Preventza<sup>1</sup>, Scott A LeMaire<sup>1</sup>, Joseph S Coselli<sup>1</sup>

<sup>1</sup>Cardiothoracic Surgery, Baylor College of Medicine, Houston, TX

**Background:** In the present study, we examined the incidence, predictors, and impact of early gastrointestinal complications (GICs) after open thoracoabdominal aortic aneurysm repair.

**Materials/Methods:** We retrospectively analyzed data from 3587 open thoracoabdominal aortic aneurysm repairs performed at our center from 1986 to 2019. We used univariate analyses and multivariable logistic regression to identify risk factors associated with GICs, including bleeding, ischemia, obstruction, and acute pancreatitis. Adverse event was defined as operative death or persistent stroke, paraplegia, paraparesis, or renal failure necessitating dialysis.

**Results:** GICs developed after 213 repairs (5.9%). GICs were less common after extent I repair than after repairs that involved infrarenal abdominal aortic segments (ie, extent II–IV;  $P = .003$ ). Patients who had GICs more often underwent interventions on the visceral arteries (51.2% vs 42.2%;  $P = .01$ ). Patients who had GICs had higher rates of operative mortality (34.3% vs 6.6%) and adverse events (44.1% vs 13.2%) and had longer hospitalization (29 vs 11 days;  $P < .001$  for all). Independent predictors of GICs included incidental splenectomy, rupture, non–extent I repair, older age, and longer aortic cross-clamp time. Survival was poorer for patients who had GICs ( $P < .001$ ).

**Conclusions:** GICs after open thoracoabdominal aortic aneurysm repair are associated with significant early and late morbidity and mortality. Development of perioperative strategies to mitigate these complications is warranted.

**Poster Number 58**

**Clinical Fellow**

**Aortopathy**

**THORACOABDOMINAL AORTIC REPAIR FOR ACUTE AND CHRONIC AORTIC DISSECTIONS**

Cuneyt Koksoy<sup>1</sup>, Vicente Orozco-Sevilla<sup>2</sup>, Qurania Preventza<sup>2</sup>, Scott A LeMaire<sup>2</sup>, Joseph S Coselli<sup>2</sup>

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**Background:** Overall outcomes after open repair of thoracoabdominal aortic aneurysms are well described, but thoracoabdominal aortic repair (TAAR) in pure aortic dissections are seldom detailed. Therefore, the objective of this study to compare the results of patients with dissection to with aneurysm without dissection who underwent TAAR.

**Materials/Methods:** From 1986 to February 2020, 1345 (37%) patients with dissection and 2309 (63%) patients with aneurysm without dissection underwent TAAR. The anatomic extent of repairs in dissections was as follows: Crawford extent I, 475 (35%), extent II, 617 (46%), extent III, 158 (12%) and extent IV 96 (7%). For aneurysms without dissections, same figures were 509 (22%), 595 (26%), 566 (25%) and 639 (28%) respectively (p<.001).

**Results:** Patients with dissection were younger (median 58 vs 70 years, P < .001). The following outcomes were recorded for the patients with dissection versus without dissection: operative mortality, 9% vs 8% (P =.3); 30-day mortality, 5% vs 6% (P =.6); persistent paraplegia, 2% vs 4 % (P = .02); renal failure necessitating hemodialysis at discharge, 5% vs 7% (P = .07); and composite adverse outcome defined as operative death, renal failure, stroke, or permanent paraplegia/paraparesis 15% vs 15% (P = .9)

**Conclusions:** Despite the more extensive aortic repair in aortic dissections, similar or better outcomes can be accomplished in comparison to outcomes of aneurysms without dissection.

## Poster Number 59

### Student

### Aortopathy

#### THORACIC AORTIC REPAIR IN PATIENTS OF JEHOVAH'S WITNESS FAITH

Rishabh Kothari<sup>1</sup>, Joseph Coselli<sup>2</sup>, Arin Jobe<sup>2</sup>, Hiruni Amarasekara<sup>2</sup>, Susan Green<sup>2</sup>, Vicente Orozco-Sevilla<sup>2</sup>, Ourania Preventza<sup>2</sup>, Scott LeMaire<sup>2</sup>

<sup>1</sup>Cardiothoracic Surgery, Baylor College of Medicine

**Background:** Cardiac and thoracic surgery in Jehovah's Witnesses (JWs) is complicated by the group's preference against receiving blood products. Although strategies and outcomes of cardiac operations in these patients have been reported, those of thoracic aortic surgery are poorly understood. We examined our experience with thoracic aortic repair in JW patients.

**Materials/Methods:** During June 1993–July 2020, 25 consecutive JW patients (median age, 57 [IQR:47–66]) underwent 30 thoracic aortic repairs (TARs) (Table 1): 17 proximal (root, ascending, arch) and 13 distal (descending thoracic, thoracoabdominal). Many repairs involved patients with heritable thoracic aortic disease (n=12; 40%) and aortic dissection (n=12; 40%). Reoperation was common (n=9; 30%), including multiple prior repairs. Repairs were often nonelective (n=12; 40%).

**Results:** Blood products were used with permission in 5 cases (17%). Three patients died postoperatively (10%): 2 after proximal TAR (12%; 1 of severe anemia and multiorgan failure, 1 of intracranial hemorrhage), and 1 after distal TAR (8%; of ruptured intracranial aneurysm after an extent II thoracoabdominal aortic aneurysm [TAAA] repair). Overall, there was 1 case of persistent paraplegia (3%; after extent II TAAA repair) and no instances of persistent ischemic stroke or renal failure.

**Conclusions:** Thoracic aortic repair in JW is complex but can be successfully performed without transfusion in most patients. Deaths and ischemic complications related to anemia appear uncommon.

**Poster Number 60**

**Junior Faculty**

**Aortopathy**

**BMPER DEFICIENCY PROTECTS PULMONARY HYPERTENSION**

Hua Mao<sup>1</sup>, Harry Karmouty-Quintana<sup>2</sup>, Christopher Ward<sup>3</sup>, Liang Xie<sup>1</sup>, Lavannya Pandit<sup>4</sup>, Xinchun Pi<sup>1</sup>

<sup>1</sup>Departments of Medicine Biochemistry and Molecular Biology, Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, X; <sup>2</sup>Michael E. DeBakey Veterans Affairs Medical Center

**Background:** The roles of BMPER( Bone morphogenetic protein (BMP)-binding endothelial regulator) in PAH and other types of pulmonary hypertension (PH) such as hypoxia and lung diseases-associated PH (Group 3) have never been studied.

**Materials/Methods:** The Group 3 PH patient whole lung samples and BMPER depletion with global or endothelial cell (EC)-specific BMPER inducible knockout (iKO) mouse models were studied.

**Results:** BMPER protein was enriched in pulmonary vasculature and its level was markedly elevated in Group 3 PH patient and mouse lungs but not in the serum. In response to 10% hypoxia for three weeks, BMPER iKO mice attenuated PH progression, indicated by decreased right ventricle (RV) systolic pressure (RVSP), RV hypertrophy (RVH) and pulmonary vascular remodeling responses. Moreover, EC-specific depletion of BMPER similarly attenuated RVSP and RVH in PH mouse models induced by hypoxia or prolyl hydroxylase 2 (PHD2) depletion, suggesting BMPER depletion plays a protective role in PH and EC is a key source for BMPER. Conversely, BMPER overexpression in pulmonary endothelium led to the spontaneous development of PH. Mechanistically, BMPER induced a potent growth factor-PDGF (platelet-derived growth factor)-D and this induction was regulated by the depletion of BMPR2 or LRP1 (LDL receptor-related protein 1), a known interacting receptor of BMPER.

**Conclusions:** BMPER in the lung is a crucial player in pulmonary vascular remodeling and upregulated in human disease and mouse hypoxic PH models.

**Poster Number 61**

**Junior Faculty**

**Aortopathy**

**SPINAL CORD DEFICIT AFTER 1114 EXTENT II OPEN THORACOABDOMINAL AORTIC ANEURYSM REPAIRS**

Vicente Orozco-Sevilla<sup>1</sup>, Joseph S Coselli<sup>1</sup>, Ourania A Preventza<sup>2</sup>, Scott A Lemaire<sup>1</sup>, Susan Green<sup>1</sup>, Ginger E Etheridge<sup>2</sup>

<sup>1</sup>Cardiothoracic Surgery, Baylor College of Medicine, Houston, TX

**Background:** We sought to examine spinal cord deficit after open extent II thoracoabdominal aortic aneurysm repair to identify predictors of the most serious type: persistent paraplegia or paraparesis

**Materials/Methods:** We included 1114 extent II thoracoabdominal aortic aneurysm repairs performed from 1991 to 2017. Intercostal/lumbar artery reattachment (n = 959, 86.1%) and cerebrospinal fluid drainage (n = 698, 62.7%) were used to mitigate the risk of postoperative spinal cord deficit. We used univariate and multivariable analyses to examine spinal cord deficit and identify predictors of persistent paraplegia or paraparesis.

**Results:** Spinal cord deficit developed after 151 (13.6%) repairs: 86 (7.7%) cases of persistent paraplegia or paraparesis (51 paraplegia; 35 paraparesis) and 65 (6.1%) cases of transient paraplegia or paraparesis. Patients with spinal cord deficit were older (median 68 vs 65 years,  $P < .001$ ) and had more rupture (6.6% vs 2.2%,  $P = .002$ ) and urgent/emergency repair (25.2% vs 16.9%,  $P = .01$ ) than those without. Persistent paraplegia or paraparesis developed immediately in 47 patients (4.2%) and was delayed in 39 patients (3.5%). Early and late survival were poorer in those with persistent paraplegia or paraparesis than in those without.

**Conclusions:** Spinal cord deficit after extent II thoracoabdominal aortic aneurysm repairs remains concerning; survival is worse in patients with persistent paraplegia or paraparesis. The complexity of spinal cord deficit and persistent paraplegia or paraparesis warrant further study.



## Poster Number 62

### Student

### Aortopathy

#### CONTEMPORARY EXPERIENCE WITH THE IMPLANTATION OR REPAIR OF HOMOGRAFTS IN 117 PROXIMAL AORTIC REPAIRS

Trung N Nguyen<sup>1</sup>, Joseph S Coselli<sup>1</sup>, Rishabh S Kothari<sup>1</sup>, Hiruni S Amarasekara<sup>1</sup>, Elizabeth Akpan-Smart<sup>1</sup>, Susan Y Green<sup>1</sup>, Ourania Preventza<sup>1</sup>, Scott A LeMaire<sup>1</sup>

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**Background:** Aortic repair with homografts is uncommon, and its durability remains uncertain. We reviewed our experience with homograft repair of the proximal aorta and open revision of failed homografts to better understand its use and durability.

**Materials/Methods:** During 1997-2018, we performed 98 primary homograft repairs of the proximal aorta and 19 open repairs of failed aortic root homografts. Infection necessitated initial homograft replacement in 71 (72%) interventions. Repair of failed homografts was most often indicated by aortic valve dysfunction. Kaplan-Meier analysis was used to estimate survival; competing risk analysis assessed the risk of homograft failure, adjusted for death.

**Results:** The median age of our cohort was 56. Of the 98 primary homografts, 89 (91%) replaced the aortic root and varying portions of the ascending aorta, 8 (12%) replaced the ascending aorta or arch, and 1 was used as a small patch. Most patients (n=84, 72%) underwent redo sternotomy. There were 13 (13%) early deaths and 8 late reoperations for homograft failure, and the 5-year survival estimate was 58.7±5.1%. When adjusted for death, the 5-year and 15-year cumulative incidence of homograft failure was 2.9% and 12.6%.

**Conclusions:** Homografts are typically reserved for complex aortic repair. Nevertheless, early and mid-term outcomes are acceptable. Homograft repairs appear reasonably durable and are corrigible after degeneration. Further study is needed to better understand their usefulness in challenging scenarios.

## Poster Number 63

### Student

### Outcomes Research

#### **DECELLULARIZED ALLOGENEIC PULMONARY ARTERY PATCHES ARE ASSOCIATED WITH LARGER PULMONARY ARTERIES AND LONGER FREEDOM FROM PULMONARY ARTERY REINTERVENTIONS**

Manasa Atyam<sup>1</sup>, Carlos Bonilla Ramirez<sup>1</sup>, Varun Aggarwal<sup>1</sup>, Athar M. Qureshi<sup>1</sup>, Jeffrey S. Heinle<sup>1</sup>, E. Dean McKenzie<sup>1</sup>

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**Background:** Although decellularized allogeneic pulmonary artery patches (DAPAP) may have the potential for recellularization and growth, they have not been consistently studied in a uniform population. We compared pulmonary artery size and reinterventions in single ventricle patients who underwent a pulmonary arterioplasty during stage II palliation with decellularized and non-decellularized allogeneic pulmonary artery patches (non-DAPAP).

**Materials/Methods:** Retrospective review identified 59 single-ventricle patients with pulmonary arterioplasty during stage II palliation (2008-2017): 28 patients underwent arterioplasty with DAPAP and 31 patients with non-DAPAP. All patients underwent pulmonary angiography during pre-Fontan catheterization at a median of 3.3 years after stage II palliation. An interventional cardiologist blinded to the place and type of pulmonary arterioplasty measured all the pulmonary arteries at standardized locations along their lengths in pre-Fontan angiograms. Pulmonary artery Z-scores at pre-Fontan angiograms and freedom from pulmonary artery reinterventions were compared between groups.

**Results:** Demographic and operative variables were similar between groups. The median follow-up time was 6.8 years (IQR 5.2, 8.60). Among 20 patients who underwent a previous Norwood procedure, a right ventricle to pulmonary artery shunt was more commonly used in the DAPAP group (12/20, 60%) and a modified Blalock-Taussig shunt was more commonly used in the non-DAPAP group (16/22, 73%). After adjusting for shunt type, the use of DAPAP was associated with higher pre-Fontan angiography Z-scores in right (estimate=0.16, standard error=0.04, p=0.001) and left pulmonary arteries (estimate=0.11, standard error=0.05, p=0.03). Patients in the DAPAP group had longer freedom from pulmonary artery reinterventions compared to patients in the non-DAPAP group (75% 42% at 7 years, p=0.014, Figure 3). After adjusting for shunt type, the use of DAPAP was associated with longer freedom from pulmonary artery reinterventions (Hazard ratio=0.38, 95% confidence interval= 0.14 - 0.99, p=0.04).

**Conclusions:** Pulmonary arterioplasty with DAPAP was associated with higher pre-Fontan pulmonary artery Z-scores and longer freedom from pulmonary artery reinterventions in a homogeneous patient population with consistent follow-up. Pulmonary artery interventions with DAPAP achieved healthy pulmonary arteries at the time of third-stage (Fontan) palliation.

**Poster Number 64**

**Postdoctoral Researcher**

**Outcomes Research**

**CORONARY ARTERY ANOMALIES ARE ASSOCIATED WITH INCREASED MORTALITY AFTER TRUNCUS ARTERIOSUS REPAIR**

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**Background:** Coronary anomalies are common in truncus arteriosus. Delineation of anatomic lesions, their relationship with mortality, and impact of surgical intervention are undefined. We identified coronary lesions in patients undergoing truncus repair, defined the impact of lesions on mortality, and studied the effect of surgical intervention of coronary lesions.

**Materials/Methods:** Coronary lesions were categorized as ostial stenosis, intramural, juxtacommissural origin, and single coronary. Survival analysis studied survival after truncus repair.

**Results:** Among 107 patients with truncus repair, 34 had at least one coronary lesion. Median follow-up time was 7 years, with 85% 5-year survival. Coronary lesions including ostial stenosis, intramurality, and juxtacommissural origin were associated with increased mortality, while single coronaries were not. Eleven patients with 1 coronary lesion and 6 patients with 2 coronary lesions had similar (80% and 83%) 5-year survival. Eight patients with 3 coronary lesions had 24% 5-year survival ( $p=0.0003$ ). Among patients with 1 or 2 lesions, coronary repair was associated with longer 5-year survival (100% vs 62%,  $p=0.06$ ). All patients with 3 lesions underwent coronary repair, with 24% 5-year survival.

**Conclusions:** Impact of coronary lesions on mortality increases with number of lesions. Coronary artery intervention is associated with improved survival in patients with 1 or 2 lesions. Patients with complex anomalies (3 lesions) have poor survival and warrant study of repair techniques.

**Poster Number 65**

**Postdoctoral Researcher**

**Outcomes Research**

**OUTCOMES IN ANOMALOUS AORTIC ORIGIN OF A CORONARY ARTERY FOLLOWING  
TRANSECTION AND REIMPLANTATION**

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**Background:** Anomalous aortic origin of a coronary artery (AAOCA) is associated with myocardial ischemia and sudden cardiac death. Although coronary unroofing is widely used, recurrent sudden cardiac death has been reported. We favor transection and reimplantation (TAR) when the anomalous coronary courses below the commissure or when unroofing would result in compression by the intercoronary pillar. Nevertheless, TAR is technically challenging and outcomes data are limited. We compared ischemia testing results and complications between patients who underwent TAR and coronary unroofing.

**Materials/Methods:** Patients presenting to the Coronary Anomalies Program (2012-2019) were managed following a standardized approach. Data were prospectively collected and compared.

**Results:** Sixty-one patients underwent surgical repair of AAOCA: 16 (26%) patients underwent TAR and 45 (74%) patients underwent unroofing. Preoperatively, 6/16 (37%) patients with a TAR and 14/45 (31%) patients with an unroofing had evidence of ischemia. One patient with TAR underwent coronary bypass grafting given persistent postoperative ischemic changes. One patient with unroofing presented with recurrent aborted sudden cardiac death and underwent subsequent TAR, without further events. At last follow-up, 1/16 patients (6%) with TAR and 7/45 (15%) patients with unroofing had evidence of ischemia.

**Conclusions:** Coronary artery TAR is a useful option when there is a course below the commissure or when unroofing would result in compression by the intercoronary pillar.

**Poster Number 66**

**Clinical Fellow**

**Outcomes Research**

**ARTIFICIAL INTELLIGENCE RELIABLY PREDICTS OUTCOMES AND COST AFTER ISOLATED CORONARY ARTERY BYPASS GRAFTING**

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**Background:** Machine learning (ML) may enhance prediction of outcomes and guide decision-making. Few reports exist applying ML to predict coronary artery bypass (CABG) outcomes at different phases of care. We sought to develop an ML model to predict CABG outcomes from pre- and intraoperative data elements.

**Materials/Methods:** STS registry data elements from 1,870 isolated CABG patients were divided into training and testing (50/50) datasets and inputted into XGBoost decision-tree algorithms. Two models were developed, one at the preoperative (80 parameters) and one at the postoperative (130 parameters) phase of care. Outcomes were operative mortality, major morbidity or mortality, high-cost, and 30-day readmission. The performance was assessed using accuracy (Acc) and the area under the curve (AUC) of the receiver operator characteristics curve and compared with STS models.

**Results:** Pre-operative models predicted mortality (Acc=97%; AUC=0.71), major morbidity or mortality (Acc=81%; AUC=0.73), high cost (Acc=73%; AUC=0.77), and 30-day readmission (Acc=69%; AUC=0.73) with high accuracy and modest AUC. Post-operative models had improved performance for all outcomes. Bypass time, cross-clamp time, and lowest temperature were consistently the most important predictive operative parameters.

**Conclusions:** ML can predict mortality, major morbidity, high cost, and readmission after isolated CABG. Prediction based on the phase of care allows for dynamic risk assessment through the hospital course, which may benefit clinical decision-making.

**Poster Number 67**

**Clinical Fellow**

**Outcomes Research**

**OUTCOMES AND RESOURCE UTILIZATION IN PATIENTS WITH HEART FAILURE AND TYPE 2 MYOCARDIAL INFARCTION**

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**Background:** Heart failure (HF) is associated with high morbidity and mortality in the United States. However, there is a paucity of data characterizing the impact of type 2 myocardial infarction (MI) in HF patients. We examined the association of type 2 MI with outcomes and resource utilization in patients hospitalized with HF.

**Materials/Methods:** The National Readmission Database was queried in 2018 for patients with primary HF hospitalizations with and without type 2 MI. Complex samples multivariable logistic and linear regression models were used to determine the association between type 2 MI and clinical outcomes (in-hospital mortality, length of stay, hospital costs, discharge to nursing facility, and 30-day readmissions).

**Results:** Of 1,072,674 HF hospitalizations included in the study, 28,813 (2.7%) had type 2 MI. Patients hospitalized for HF with type 2 MI had significantly higher in-hospital mortality (adjusted odds ratio [aOR], 1.53; 95% CI, 1.37-1.72), hospital costs (adjusted parameter estimate [aPE], \$1,785; 95% CI, 1,388-2,182), rate of discharge to nursing facility (aOR, 1.22; 95% CI, 1.15-1.29), longer LOS (aPE, 0.53; 95% CI, 0.42-0.64), and rate of 30-day all-cause readmissions (aOR, 1.06; 95% CI, 1.01-1.12). Sub-group analyses were concordant with the main analyses.

**Conclusions:** Type 2 MI in patients hospitalized with HF is associated with higher mortality and resource utilization. This study adds the growing evidence that type 2 MI contributes to poor outcomes for acute HF hospitalizations.

**Poster Number 68**

**Postdoctoral Researcher**

**Outcomes Research**

**EFFICACY OF TELEREHABILITATION ON MOBILITY AND FRAILTY IN VETERANS WITH CHRONIC HEART AND LUNG DISEASE**

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**Background:** Congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) affect millions of Americans, and are leading causes of death in the United States. Decreased mobility, often measured with 6-minute walk distance, is a key feature in CHF and COPD, and has been often a primary outcome in many clinical trials. Additionally, emerging evidence suggests frailty, defined as decrease in physiological reserve, is prevalent in patients with CHF and COPD. Although frailty is now considered a reversible and manageable condition, evidence on frailty from clinical trials is sparse. We aimed to investigate the efficacy of 12-week cardiopulmonary telerehabilitation on 6-minute walk distance and frailty status in patients with CHF and COPD.

**Materials/Methods:** Veterans with CHF or COPD (n = 41 [39 men]; age =  $68.1 \pm 8.7$  years; body-mass index =  $30.06 \pm 5.34$  kg/m<sup>2</sup>; forced volume in one second [FEV1] =  $46 \pm 15\%$ ; forced volume in one second/forced vital capacity [FEV1/FVC] =  $53 \pm 14\%$ ; oxygen saturation [SPO2] =  $93 \pm 3\%$ ) participated after signing a written informed consent. Participants received exercise treatment (3 sessions per week; 2 hours per session) composed of strengthening and balance exercise, respiratory exercise and smoking and dietary education provided by the study physical therapist (MSB) and respiratory therapist (CN) through Veterans Affairs telehealth service. Outcome measures were 6-minute walk distance (exercise capacity measure) and Fried frailty phenotype (vulnerability measure).

**Results:** Across all participants, 6-minute walk distance increased from  $262.91 \pm 76.02$  meters to  $304.18 \pm 84.60$  meters after the telerehabilitation program (15.7% improvement;  $p < 0.001$ ; medium effect size). For frailty status, compared to baseline (6 non-frail; 35 frail), eight more Veterans (19.5% of all participants) were classified as non-frail after the telerehabilitation program (14 non-frail; 27 frail), however, these improvements did not reach a statistically significant level ( $p = 0.069$ ).

**Conclusions:** The 12-week cardiopulmonary telerehabilitation is effective in improving exercise capacity and may also be effective in treating vulnerability in Veterans with CHF or COPD.

**Poster Number 69**

**Postdoctoral Researcher**

**Outcomes Research**

**INSTITUTIONAL EXPERIENCE OF EXTRACORPOREAL MEMBRANE OXYGENATION AND LEFT VENTRICULAR DECOMPRESSION USING THE IMPELLA VENTRICULAR ASSIST DEVICE**

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**Background:** Cardiogenic shock (CS) has a high mortality and morbidity rate across pediatric age groups. The Impella percutaneous assist device (PVAD) is minimally invasive and provides direct LV unloading in setting of VA-ECMO support. We report our pediatric center's experience with ECMO and Impella PVAD in the setting of refractory CS

**Materials/Methods:** Retrospective analysis of Impella PVAD in setting of peripheral ECMO support for CS. Data presented as mean (SD), median (IQR) and proportion (%). Differences calculated using t-tests

**Results:** 13 patients age 13.3 (SD:  $\pm 3.7$ ) years, weight 55.0 (SD:  $\pm 21.7$ ) kg, and BSA 1.5 (SD:  $\pm 0.3$ ) m<sup>2</sup> underwent PVAD and ECMO for CS. PVAD preceded ECMO in 4 patients (30.8%), ECMO was added to PVAD in 9 patients (69.2%). Median length of support was 6 days (IQR: 3.3 – 8.7) in Impella-ECMO cohort, and 5 days (IQR: 2 – 7 days) for ECMO-Impella cohort. Device complications included site bleeding (61.5%) and malfunction (38.5%). Patient complications included arrhythmia (61.5%) and hemolysis (61.5%). Median length of hospital stay was 35 days (IQR: 7 – 63). Mean capillary wedge pressures decreased by 9.3 mmHg before and after support (23.3 vs 14 mmHg,  $p = 0.0134$ ). Survival to hospital discharge was 69.2%

**Conclusions:** We describe the first pediatric experience using the Impella PVAD device in setting of ECMO. The Impella device can work as complementary support for LV unloading in setting of VA-ECMO in older pediatric population with CS. This carries low stroke risk and satisfactory survival benefit.



## Poster Number 70

### Student

### Outcomes Research

#### **PROPENSITY SCORE MATCHED ANALYSIS OF OUTCOMES, COST, AND READMISSIONS AFTER CORONARY ARTERY BYPASS GRAFTING AT SAFETY NET HOSPITALS IN THE UNITED STATES**

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**Background:** We hypothesized that SNHs would have higher observed morbidity, mortality, costs, and readmissions after coronary artery bypass grafting (CABG) than non-SNHs, but equivalent outcomes when comparing matched populations in a nationwide sample.

**Materials/Methods:** The National Readmissions Database (2016–2018) was queried for patients undergoing isolated CABG. Safety net burden was defined as percentage of all admissions who were uninsured or Medicaid, with hospitals in the top quartile defined as SNHs. Outcomes were adjusted for patient and hospital characteristics using propensity score matching.

**Results:** A total of 542,448 patients underwent CABG, including 101,966 (19%) at SNHs. Patients at SNHs were younger (65 vs 66 years), more complex (median Elixhauser score 7 vs 6), more frequently from the lowest income quartile (33.2% vs 26.4%), and more frequently required urgent surgery (57.9% vs 53.3%) (all  $p < 0.001$ ). Observed mortality (2.3% vs 1.9%), costs (\$57,158 vs \$47,870) and 30-day readmissions (11.6% vs 10.6%) were greater at SNHs (all  $p < 0.001$ ). After propensity score matching to create 59,575 matched pairs, rates of in-hospital mortality, major morbidity, and readmissions at SNHs were comparable or better than rates at non-SNHs; however, SNHs had higher costs (\$57,121 vs \$50,766), potentially from longer LOS (11.1 vs 10.8 days) (all  $p < 0.001$ ).

**Conclusions:** SNHs perform CABG on higher risk patients with comparable outcomes to non-SNHs. Strategies to reduce LOS should be pursued to reduce costs at SNHs.

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