

11TH ANNUAL SYMPOSIUM
Cardiovascular Research Institute

APRIL 10, 2024



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ABOUT THE CVRI

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. The CVRI aims to provide administrative and research support to promote synergy for interdisciplinary basic, translational, and clinical research.

COMMITTEE CHAIR



Lilei Zhang, M.D., Ph.D.
Associate Professor
Molecular and Human Genetics
Baylor College of Medicine

SYMPOSIUM & SEMINAR COMMITTEE

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William Lagor, Ph.D.

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Jing Liu, M.D.

A.J. Marian, M.D.

Dianna Milewicz, M.D., Ph.D.

Jack Price, M.D.

Jeff Steimle, Ph.D.

Xander Wehrens, M.D., Ph.D.

Richelle Lopez

Sandra Guerra

SESSION CHAIRS

SESSION I Liang Xie, Ph.D.

SESSION II Xander Wehrens, M.D., Ph.D.

SESSION III Lilei Zhang, M.D., Ph.D.

SESSION IV Ali J. Marian, M.D.

FROM THE DIRECTOR



Dear Colleagues,

It is with great pleasure that I welcome you to the 11th Annual Symposium of the Cardiovascular Research Institute (CVRI) at Baylor College of Medicine.

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 in the Texas Medical Center. The CVRI is also actively expanding training programs in cardiovascular sciences. We are excited that a new T32-funded training program in 'Cardiovascular Research and Drug Development' will start in July of this year.

This year CVRI is honored to feature distinguished keynote Andrew Marks, M.D. Dr. Marks is Chair and Professor of the Physiology and Cellular Biophysics Department at Columbia University and will speak on "Leaky ryanodine receptors provide clues for treating disorders of heart, muscle and brain". He is a member of the National Academy of Sciences (2005), National Academy of Medicine (2004), and American Academy of Arts and Sciences (2005). From 2002 to 2007 Dr. Marks was Editor-in-Chief of the Journal of Clinical Investigation. Dr. Marks' research has published over 290 articles in which he has contributed new understandings of fundamental mechanisms that control muscle contraction, heart function, lymphocyte activation, and cognitive function. He has discovered novel causes of human diseases linked to leaky ryanodine receptor (RyR)/calcium release channels including heart failure, cardiac arrhythmias, muscular dystrophy, diabetes, and neurodegenerative disorders. He has developed novel treatments for coronary artery disease (in 2003 the FDA approved the first drug eluting stent), and a new class of drugs called Rycal® that fix RyR channel leak. A Rycal® is in clinic trials for myopathies and cardiac arrhythmias.

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

Sincerely,

A handwritten signature in blue ink, appearing to read 'Xander Wehrens', with a stylized flourish at the end.

Xander Wehrens, M.D., Ph.D.
Director, Cardiovascular Research Institute
Baylor College of Medicine

CME INFORMATION

NEEDS STATEMENT

There is a critical need to address the rapidly evolving landscape of medical research and technology, particularly in the field of cardiovascular health. As medical research and technology change rapidly, it is increasingly important for physicians, Ph.D. faculty, residents, fellows, medical students, graduate school trainees, and other healthcare professionals to stay informed of new evidence. This symposium is designed as a platform to share and discuss state-of-the-art ongoing, innovative, and new cardiovascular research with the ultimate goal of translating research into clinical practice. Despite the abundance of new findings and technologies, there exists a knowledge gap among healthcare professionals regarding the latest developments in cardiovascular research and their application in clinical settings. Newly learned pathways can serve as potential mechanisms and alternative strategies in new research applications, but without awareness and understanding among healthcare professionals, these advancements may not be effectively integrated into patient care. Additionally, topics on how to apply new diagnostic and imaging techniques can create opportunities for collaboration with the developers of these techniques in new research protocols, fostering a multidisciplinary approach to improving cardiovascular care. Therefore, there is a critical need to address the knowledge gap and equip healthcare professionals with the necessary

TARGET AUDIENCE

This activity is for Physicians, Fellows, Residents, Trainees, Physician Assistants, and Nurses/Nurse Practitioners specializing in cardiovascular research and care, and all other practitioners interested in cardiovascular sciences.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the participant should be able to:

- Identify risk modifications in congenital heart disease.
- Analyze gene editing-based approaches.
- Evaluate the role of fibrinogen in thromboinflammation.
- Interpret the role of vascular endothelium in metabolic homeostasis.

EDUCATIONAL METHODS

Lecture and Question & Answer

EVALUATION

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

CME INFORMATION

ACCREDITATION/CREDIT DESIGNATION

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

Baylor College of Medicine designates this live activity for a maximum of 3.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

OBTAINING CREDIT

Two (2) business days after the course, an email will follow from the Baylor College of Medicine, Division of Continuing Professional Development with instructions for completing the evaluation and obtaining your CME Certificate, CE Certificate, or Certificate of Attendance.

Contact Information

Baylor College of Medicine
Division of Continuing Professional Development
One Baylor Plaza, MS: BCM 155
Houston, TX 77030-3411

Email: cpd@bcm.edu
Phone: 713.798.8237
Fax: 713.798.7955

Visit our website at cpd.education.bcm.edu for information about additional CME activities.

DRUG/DEVICE STATUS DISCLOSURE

Some drugs/devices identified during this activity may have United States Food and Drug Administration (FDA) clearance for specific purposes only or for use in restricted research settings. The FDA has stated that it is the responsibility of the individual physician to determine the FDA status of each drug or device that he/she wishes to use in clinical practice and to use the products in compliance with applicable law.

Baylor College of Medicine requires that all faculty/presenters disclose an unlabeled use or investigational use of pharmaceutical and medical device products, and provide adequate scientific and clinical justification for such use. Physicians are urged to fully review all the available data on products or procedures before using them to treat patients.

CME INFORMATION

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH COMMERCIAL INTERESTS

DISCLOSURE POLICY

Baylor College of Medicine (BCM) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education (CME) for physicians. BCM is committed to sponsoring CME activities that are scientifically based, accurate, current, and objectively presented.

In accordance with the ACCME Standards for Commercial Support, BCM has implemented a mechanism requiring everyone in a position to control the content of an educational activity (i.e., directors, planning committee members, faculty) to disclose any relevant financial relationships with commercial interests (drug/device companies) and manage/resolve any conflicts of interest prior to the activity. Individuals must disclose to participants the existence or non-existence of financial relationships at the time of the activity or within 24 months prior.

In addition, BCM has requested activity faculty/presenters to disclose to participants any unlabeled use or investigational use of pharmaceutical/device products; to use scientific or generic names (not trade names) in referring to products; and, if necessary to use a trade name, to use the names of similar products or those within a class. Faculty/presenters have also been requested to adhere to the ACCME's validation of clinical content statements.

BCM does not view the existence of financial relationships with commercial interests as implying bias or decreasing the value of a presentation. It is up to participants to determine whether the relationships influence the activity faculty with regard to exposition or conclusions. If at any time during this activity you feel that there has been commercial/promotional bias, notify the Activity Director or Activity Coordinator. Please answer the questions about balance and objectivity in the activity evaluation candidly.

All of the relevant financial relationships listed for these individuals have been mitigated.

CME INFORMATION

DISCLOSURES

FACULTY	PLANNING COMMITTEE	PRESENTER	DISCLOSURE
Gang Bao, Ph.D. Foyt Family Professor Rice University		●	Nothing to disclose
Biykem Bozkurt, M.D., Ph.D. Associate Director of Cardiovascular Research Institute Baylor College of Medicine		●	Type of financial relationship: Consultant, Ineligible companies: Bayer, Astra Zeneca, Sanofi, sc Pharma, Abbott, Vifor, Zoll/ Respicardia, Topic: Heart Failure
Miguel Cruz, Ph.D. Professor and Division Chief Baylor College of Medicine		●	Nothing to disclose
Bhanu Ganesh, Ph.D. Assistant Professor McGovern Medical School		●	Nothing to disclose
Sandra Guerra Sr. Business Operations Associate Cardiovascular Research Institute Baylor College of Medicine	●		Nothing to disclose
Jason Karch, Ph.D., BA Assistant Professor Baylor College of Medicine		●	Nothing to disclose
Peter Lillehoj, Ph.D. Associate Professor Rice University		●	Nothing to disclose
Richelle Lopez Senior Coordinator, Business Operations Baylor College of Medicine	●		Nothing to disclose
Andrew Marks, M.D. Professor and Chair Department of Physiology and Cellular Biophysics Columbia University		●	Type of financial relationship: Board Membership, Ineligible company: ARMGO Pharma, Topic: RyR Therapeutics
Christina Miyake, M.D., M.S. Associate Professor in the Department of Molecular Physiology and Biophysics Baylor College of Medicine		●	Nothing to disclose
Shaine Morris, M.D., M.P.H. Associate Professor Baylor College of Medicine		●	Type of financial relationship: Consultant, Ineligible company: Ayti Biopharma, Topic: Vascular EDS Trial.
Xinchun Pi, Ph.D. Associate Professor Cardiovascular Research Institute Baylor College of Medicine		●	Nothing to disclose
Xander Wehrens, M.D., Ph.D. – Activity Director Professor Baylor College of Medicine	●		Type of financial relationship: Consultant, Ineligible company: Rocket Pharmaceuticals, Topic: Heart Disease.

CME INFORMATION

DISCLAIMER

This activity is designed for healthcare professionals for educational purposes. Information and opinions offered by the faculty/presenters represent their own viewpoints. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information.

While Baylor College of Medicine makes every effort to have accurate information presented, no warranty, expressed or implied, is offered. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decisionmaking before applying any information, whether provided here or by others, for any professional use.

Faculty/presenters have submitted materials for this syllabus for printing in advance so that you may have an outline or summary of the main points of their presentation. Often this differs from the final version of their slides as faculty/ presenters make revisions up until the day of the meeting.

Additionally, some images (cartoons, drawings and some photographs) shown on the screen may not be present in your educational materials because of publishers' requirements for reprinting of copyrighted images.

NOTICES

Faculty, topics, program schedule, and credit are subject to change.

Audio or videotaping is prohibited without written permission from the Activity Directors and the Division of Continuing Professional Development, Baylor College of Medicine, Houston, Texas.

DR. MARK L. ENTMAN AWARD FOR EXCELLENCE IN CARDIOVASCULAR EDUCATION



Mark L. Entman, M.D.
Distinguished Professor
Emeritus of Medicine,
Biochemistry and Pathology
Baylor College of Medicine

The Dr. Mark L. Entman Award for Excellence in Cardiovascular Education was established in 2021 by the Cardiovascular Research Institute (CVRI) at Baylor College of Medicine to recognize faculty members for outstanding teaching and service in the graduate school curriculum.

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

Dr. Entman was recruited to Baylor as an Assistant Professor in 1970. He was a Howard Hughes Medical Investigator from 1971 to 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 to 1985. 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 Baylor faculty, Dr. Entman's training at Duke University involved matriculation in the highly innovative Research Training Program designed to promote the proper background for cellular and molecular research for M.D.'s 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 M.D./Ph.D. 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 Ph.D. 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.

SPEAKERS



Gang Bao, Ph.D.

Chair and Professor of Bioengineering
Department of Bioengineering
Rice University



Biykem Bozkurt, M.D., Ph.D.

Senior Dean of Faculty
Professor of Medicine
Baylor College of Medicine
Medical Care Line Executive
Michael E. DeBakey VA Center



Miguel A. Cruz, Ph.D.

Chief, Division of Thrombosis Research
Professor of Medicine
Baylor College of Medicine



Bhanu Priya Ganesh, Ph.D.

Assistant Professor of Neurology
University of Texas Health Science Center
McGovern Medical School



Jason M. Karch, Ph.D.

Assistant Professor of Integrative Physiology
Baylor College of Medicine

SPEAKERS



Peter B. Lillehoj, Ph.D.

Associate Professor of Mechanical Engineering & Bioengineering
Rice University



Christina Y. Miyake, M.D., M.S.

Associate Professor of Pediatric Cardiology
Texas Children's Hospital
Associate Professor of Integrative Physiology
Baylor College of Medicine



Shaine A. Morris, M.D., M.P.H.

Pediatric Cardiologist
Texas Children's Hospital
Associate Professor of Pediatrics - Cardiology
Baylor College of Medicine



Xinchun Pi, Ph.D.

Associate Professor of Medicine - Athero & Lipo
Baylor College of Medicine

AGENDA

11TH ANNUAL SYMPOSIUM Cardiovascular Research Institute

APRIL 10, 2024

8:00 – 8:30 a.m. **Registration**

8:30 – 8:40 a.m. **Welcome & Opening Remarks**

Xander Wehrens, M.D., Ph.D.

Director, Cardiovascular Research Institute

Professor of Integrative Physiology

Baylor College of Medicine

8:40 – 10:00 a.m. **Session I**

Moderator: Liang Xie, Ph.D.

Assistant Professor of Medicine – Athero & Lipo

Baylor College of Medicine

8:40 – 9:00 a.m. **“Gene Editing Based Approaches for Treating Sickle Cell Disease”**

Gang Bao, Ph.D.

Chair and Professor of Bioengineering

Department of Bioengineering

Rice University

9:00 – 9:20 a.m. **“A Closer Look at Fibrinogen in Thromboinflammation”**

Miguel A. Cruz, Ph.D.

Professor of Medicine - Thrombosis

Baylor College of Medicine

9:20 – 9:40 a.m. **“Gut-Brain Axis in Post-Stroke Inflammation”**

Bhanu Priya Ganesh, Ph.D.

Assistant Professor of Neurology

UT Health Science Center at Houston

McGovern School of Medicine

9:40 – 10:00 a.m. **“Microfluidic Technologies for Medical Diagnostics and Global Health”**

Peter B. Lillehoj, Ph.D.

Chair and Professor of Mechanical Engineering

Rice University

10:00 – 11:00 a.m. **Poster Session I**

AGENDA

11:00 a.m. – noon Session II

Moderator: Xander Wehrens, M.D., Ph.D.

Professor of Integrative Physiology
Director, Cardiovascular Research Institute
Baylor College of Medicine

11:00 a.m. – noon KEYNOTE

“Leaky Ryanodine Receptors Provide Clues for Treating Disorders of Heart, Muscle and Brain”

Andrew Marks, M.D.

Chair and Professor of Physiology and Molecular Biophysics
Columbia University

noon – 1:30 p.m. Poster Session II & Lunch

1:30 – 2:30 p.m. Session III

Moderator: Lilei Zhang, M.D., Ph.D.

Associate Professor of Molecular and Human Genetics
Baylor College of Medicine

1:30 – 1:50 p.m. “Understanding Risk Modification in Left-Sided Congenital Heart Disease” **Shaine A. Morris, M.D., M.P.H.**

Pediatric Cardiologist
Texas Children’s Hospital
Associate Professor of Pediatrics - Cardiology
Baylor College of Medicine

1:50 – 2:10 p.m. “Current Epidemiology and Treatment of Heart Failure” **Biykem Bozkurt, M.D.**

Senior Dean of Faculty
Associate Director, CVRI

2:10 – 2:30 p.m. “Saving Lives in TANGO2 Deficiency Disorder - Collaborative and Translational Bedside to Bench back to Bedside Research”

Christina Miyake, M.D., M.S.

Associate Professor and Director of the Cardiovascular Genetics Arrhythmia Program
Texas Children’s Hospital
Associate Professor of Physiology and Biophysics
Baylor College of Medicine

2:30 – 3:15 p.m. Poster Session III

AGENDA

3:15 – 4:30 p.m.

Session IV

Moderator: Ali J. Marian, M.D.

Professor of Molecular Medicine and Internal Medicine (Cardiology)
University of Texas Health – McGovern School of Medicine

3:35 – 3:55 p.m.

“Decipher the Secretive Role of the Vascular Endothelium in Metabolic Homeostasis”

Xinchun Pi, Ph.D.

Associate Professor of Medicine
Baylor College of Medicine

3:55 – 4:15 p.m.

“Triggering the Mitochondrial Permeability Transition Pore”

Jason Karch, Ph.D.

Assistant Professor of Integrative Physiology
Baylor College of Medicine

4:15 – 4:30 p.m.

Awards Ceremony & Closing Remarks

Lilei Zhang, M.D., Ph.D.

Xander HT Wehrens, M.D., Ph.D.

4:30 – 5:15 p.m.

Reception & Poster Viewing

KEYNOTE SPEAKER

ANDREW R. MARKS, M.D.



Andrew R. Marks, M.D.
Chair and Professor of
Physiology and Cellular
Biophysics
Columbia University

Andrew R. Marks, M.D. is Chair and Professor of the [Physiology and Cellular Biophysics Department at Columbia University](#). He is a member of the [National Academy of Sciences](#) (2005), National Academy of Medicine (2004), and American Academy of Arts and Sciences (2005). From 2002 to 2007 Dr. Marks was [Editor-in-Chief](#) of the *Journal of Clinical Investigation*. Dr. Marks' research has published over [290 articles](#) in which he has contributed new understandings of fundamental mechanisms that control muscle contraction, heart function, lymphocyte activation, and cognitive function. He has discovered novel causes of human diseases linked to leaky ryanodine receptor (RyR)/calcium release channels including heart failure, cardiac arrhythmias, muscular dystrophy, diabetes, and neurodegenerative disorders. He has developed novel treatments for coronary artery disease (in 2003 the FDA approved the first drug eluting stent), and a new class of drugs called Rycal® that fix RyR channel leak. A Rycal® is in clinic trials for myopathies and cardiac arrhythmias.

Andrew R. Marks, M.D., received his undergraduate degree from Amherst College where he was the first student in the history of the college to graduate with honors in two subjects (Biology and English), and his M.D. from Harvard Medical School in 1980. Following an internship and residency in internal medicine at the Massachusetts General Hospital (MGH), he was a post-doctoral fellow in molecular genetics at Harvard Medical School, and then a clinical cardiology fellow at the MGH. In 1987 Dr. Marks joined the Cardiology Division at the Brigham and Women's Hospital. He then moved back to his hometown, New York, in 1990, as an Assistant Professor of Molecular Biology and Medicine at Mount Sinai School of Medicine. In 1995 he was named the Fishberg Professor of Medicine at Mount Sinai, and in 1997 he moved to Columbia University College of Physicians & Surgeons as Director of the Center for Molecular Cardiology and the Clyde and Helen Wu Professor of Medicine and Pharmacology. In 2003 Dr. Marks was appointed Chair and Professor of the Physiology and Cellular Biophysics Department at Columbia University. From 1997 to 2000 he was a member of the ASCI Council, and from 2002 to 2007 Dr. Marks was Editor-in-Chief of the *Journal of Clinical Investigation*. His honors include the Established Investigator Award and the Basic Research Prize from the American Heart Association, the Distinguished Clinical Scientist Award of the Doris Duke Charitable Foundation, the Dean's Distinguished Lecturer in Basic Science at Columbia, and memberships in the American Society of Clinical Investigation, the American Association of Physicians, the Institute of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences. He has received the Doctor of Science Honoris Causa from Amherst College (2009), the ASCI Stanley J. Korsmeyer Award (2010) and the Pasarow Foundation Award for Cardiovascular Research (2011). Dr. Marks is a member of the advisory committee of the

KEYNOTE SPEAKER

ANDREW R. MARKS, M.D.

Gladstone Institute for Cardiovascular Disease and has served on the NHLBI Advisory Council, the Centocor SAB and the Novartis Science Board. Dr. Marks is chair of the SAB of ARMGO Pharma, Inc. a company he founded in 2006 to develop novel therapeutics for heart and muscle diseases and is the inventor on six U.S. patents for these new treatments. In 2001 he founded the Summer Program for Under-represented Students (SPURS) at Columbia. SPURS provides mentored research training at Columbia University for minority students from the NY City public colleges and universities.

Dr. Marks' work on the mechanisms of action of drugs that inhibit vascular smooth muscle proliferation and migration has been translated into novel therapeutics including drug-eluting stents for treatment of coronary artery disease that have substantially reduced the incidence of in-stent restenosis, as well as effective therapy to reduce accelerated arteriopathy following cardiac transplantation. Dr. Marks has defined how macromolecular signaling complexes regulate ion channel function in muscle and non-muscle systems. His work has contributed new understandings of fundamental mechanisms that regulate muscle contraction. He discovered that "leaky" intracellular calcium release channels (ryanodine receptors) contribute to heart failure, fatal cardiac arrhythmias, and impaired exercise capacity particularly in muscular dystrophy. Dr. Marks discovered a new class of small molecules (Rycals) developed in his laboratory, that effectively treat cardiac arrhythmias, heart failure and muscular dystrophy in pre-clinical studies. His new approach, based on fixing the "leak" in the ryanodine receptor/calcium release channels, is in Phase II clinical trials for the treatment of heart failure, and cardiac arrhythmias, and is being developed for the treatment of muscular dystrophy.

SPEAKER BIOGRAPHIES



Gang Bao, Ph.D.

Chair and Professor of Bioengineering
Department of Bioengineering
Rice University

Dr. Gang Bao is Chair of the Department of Bioengineering and the Foyt Family Professor at Rice University. He is also a CPRIT Senior Scholar in Cancer Research and the Director of Nanomedicine Center for Nucleoprotein Machines at Rice. Dr. Bao received his undergraduate and Master's degrees from Shandong University in China, and his Ph.D. from Lehigh University in the U.S. Dr. Bao is a Fellow of the American Association of Advancement in Science (AAAS), American Society of Mechanical Engineers (ASME), American Physical Society (APS), American Institute for Medical and Biological Engineering (AIMBE), and Biomedical Engineering Society (BMES). Dr. Bao has published more than 240 peer-reviewed journal papers. Dr. Bao's current research is focused on the development of nanomedicine and genome engineering tools and approaches for biological and disease studies, including multifunctional magnetic nanoparticles, protein targeting and quantification methods, and engineered nucleases such as CRISPR/Cas9. These approaches have been applied to the diagnosis and treatment of chronic diseases such as cancer and cardiovascular disease, and the development of genome editing approaches for treating single-gene disorders including sickle cell disease and cystic fibrosis.



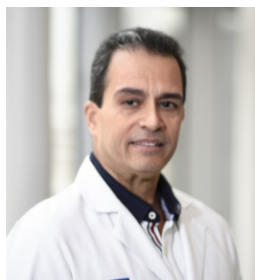
Biykem Bozkurt, M.D., Ph.D.

Senior Dean of Faculty
Professor of Medicine
Baylor College of Medicine
Medical Care Line Executive
Michael E. DeBakey VA Center

Dr. Biykem Bozkurt is the Senior Dean of Faculty at Baylor College of Medicine; Mary and Gordon Cain Chair and Professor of Medicine; Director of Winters Center of Heart Failure; W.A. "Tex" and Deborah Moncrief, Jr., Chair and Medicine Chief at the Michael E. DeBakey VA Medicine in Houston. She also serves as the Associate Director of the Cardiovascular Research Institute. Throughout her career, Dr. Bozkurt has been recognized for excellence in clinical care, education, and research. She was the recipient of the VA career development grant and MERIT research awards, American College of Cardiology Proctor Harvey MD Young Teacher Award, American College of Cardiology Gifted Educator Award, Baylor College of Medicine presidential awards in Education, Lifetime Master Clinician, and Professionalism. She has been listed in Clarivate World's Highly Cited Researchers (top 1% Web of Science) in 2018, 2019 and 2020.

She is the Editor-in-Chief of JACC: Heart Failure and served as the President of the Heart Failure Society of America in 2019–2020. She led the Universal Definition and Classification of Heart Failure as the Chair in 2021, and the Vice-Chair of the 2022 AHA/ACC Heart Failure Guidelines Writing Committee. Dr. Bozkurt actively participates in clinical and translational research; provides advanced heart failure patient care; presents at national and international scientific sessions; teaches and mentors trainees and faculty.

SPEAKER BIOGRAPHIES



Miguel A. Cruz, Ph.D.

Chief, Division of Thrombosis Research
Professor of Medicine
Baylor College of Medicine

Dr. Miguel A. Cruz is a protein biochemist. He graduated with Ph.D. from the University of Puerto Rico-Medical Science Campus, Rio Piedras, Puerto Rico. Dr. Cruz completed post-doctoral training at Harvard Medical School, Boston. His research focuses on the pathophysiology of thrombosis, with an emphasis

on the molecular mechanisms by which the protein von Willebrand factor (VWF) mediates platelets adhesion that leads to thrombus formation in clinical conditions such as myocardial infarction, stroke, TBI and sepsis. Dr. Cruz's group has identified key structural mechanisms that regulate the interaction of the protein VWF with flowing platelets under high hemodynamic forces. In addition, he has discovered novel ligands for VWF that are involved in thromboinflammation. Among his contributions is the development of a potential therapeutic compound to prevent microvascular thrombosis and TBI-associated coagulopathy.



Bhanu Priya Ganesh, Ph.D.

Assistant Professor of Neurology
University of Texas Health Science Center
McGovern Medical School

Dr. Bhanu Priya Ganesh is an Assistant Professor in the Department of Neurology at the University of Texas Health Science Center at Houston McGovern Medical School. Dr. Ganesh received her Ph.D. under the supervision of Dr. Michael Blaut from the German Institute of Human Nutrition-

Potsdam Rehbruecke (DIfE), Leibniz institute, Germany from 2010 to 2014. Shortly thereafter, she relocated to Houston for her post-doctoral training where she was trained by Dr. James Versalovic in the Department of Pathology and Immunology at Baylor College of Medicine from 2014 to 2017. She in-between held a visiting scientist position at Massachusetts Institute of Technology (MIT), Cambridge from 2014 to 2016 where she was trained by Dr. James Fox. After post-doctoral training at Baylor, she joined the department of Neurology (BRAINS lab) led by Dr. Louise McCullough at University of Texas Health Science Center Houston (UTHSC) as a senior postdoctoral fellow from 2017 to 2018. In 2018, she was promoted as an Assistant Professor in the department of Neurology. Currently, her primary interest lies on investigating signaling mechanisms involved in gut-brain axis interactions in aging-associated cerebrovascular diseases especially, stroke, Alzheimer's disease, Cerebral Amyloid Angiopathy, Neonatal Hypoxic encephalopathy at UTHSC.

SPEAKER BIOGRAPHIES



Jason M. Karch, Ph.D.

Assistant Professor of Integrative Physiology
Baylor College of Medicine

Dr. Jason Karch is an Assistant Professor in the Integrative Physiology department at Baylor College of Medicine. He has garnered acclaim for his pioneering contributions to the understanding of cell death pathways, particularly in the context of myocardial infarctions. Following the completion of his Ph.D. in Cancer and Cell Biology from the University of Cincinnati under the esteemed mentorship of Dr. Jeffery Molkentin in 2012, Dr. Karch continued as a post-doctoral HHMI fellow, delving deeper into the intricate realms of mitochondrial dysfunction and cardiac biology. In 2019, Dr. Karch's scholarly journey culminated in the establishment of his own laboratory at Baylor College of Medicine, where he leads a team of dedicated researchers in unraveling the mysteries of cardiac cell death pathways, with a keen focus on the enigmatic mitochondrial permeability transition pore. Dr. Karch's overall goal is to develop targeted therapeutic interventions aimed at preserving the viability and functionality of heart cells following ischemic events.



Peter B. Lillehoj, Ph.D.

Associate Professor of Mechanical Engineering & Bioengineering
Rice University

Dr. Peter Lillehoj is an Associate Professor of Mechanical Engineering and Bioengineering and holds the Shankle Chair in Mechanical Engineering at Rice University. Prior to joining Rice, he was a faculty member in Mechanical Engineering and Biomedical Engineering at Michigan State University (MSU). He received a B.S. degree in Mechanical Engineering in 2006 from Johns Hopkins University and M.S. and Ph.D. degrees in Mechanical Engineering from the University of California, Los Angeles in 2008 and 2011, respectively. Dr. Lillehoj has made significant contributions in the areas of microfluidic biosensors, mobile phone-based diagnostics and wearable biosensors, and his research has been featured in various news media, including The Huffington Post, The Gates Notes, CBS, and Gizmodo. He is a recipient of the NSF CAREER Award in 2014, IEEE New Innovator in NANOMED Award in 2019, Wellcome Trust Innovator Award in 2020, and two Grand Challenges Explorations grants from the Bill & Melinda Gates Foundation. He is a member of the American Society of Mechanical Engineers, the Biomedical Engineering Society and the Institute of Electrical and Electronic Engineers and is an Editorial Board member for Scientific Reports.

SPEAKER BIOGRAPHIES



Christina Y. Miyake, M.D., M.S.

Associate Professor of Pediatric Cardiology
Texas Children's Hospital
Associate Professor of Integrative Physiology
Baylor College of Medicine

Dr. Christina Miyake is an Associate Professor and Director of the Cardiovascular Genetics Arrhythmia Program at Texas Children's Hospital and Associate Professor in the Department of Integrative Physiology at Baylor College of Medicine. She is also a member of the Arrhythmia and Pacing (Electrophysiology) Service and leads the interdisciplinary TANGO2 team at Texas Children's Hospital. She specializes in the care of pediatric patients and their families with heritable cardiac arrhythmia disorders, with a special interest in patients who have no diagnosis. She is actively involved in translational research, collaborating with several Baylor labs including the Wehrens, Zhang, and Li labs, focusing on identifying the molecular basis of heritable arrhythmia disorders and translating these findings between clinical and basic research. Her research has helped to discover and describe new heritable disorders such as TANGO2 Deficiency Disorder and EXOSC5 and expand upon several known disorders such as Catecholaminergic Polymorphic Ventricular Tachycardia, Brugada Syndrome, and Arrhythmogenic Cardiomyopathy. Her long-term goal is to leverage her clinical, basic, and genetic expertise to advance treatment and improve the quality of care and outcomes among patients with arrhythmia disorders.



Xinchun Pi, Ph.D.

Associate Professor of Medicine – Athero & Lipo
Baylor College of Medicine

Dr. Xinchun Pi is an Associate Professor in the Division of Cardiovascular Research at Baylor College of Medicine. She received her Ph.D. in Pharmacology from the University of Rochester in New York in 2004. Her studies focus on the molecular mechanisms underneath the regulation of endothelial cell functions during vascular development and a variety of pathological conditions such as inflammation, atherosclerosis, peripheral vascular disease, cancer, diabetes, and obesity. Her particular focus is to understand the signaling pathways associated with endothelial function that are critical in order to develop treatments for these vascular-associated conditions. Particular attention is directed toward LRP1 (low density lipoprotein receptor-related protein 1) and Bmper (Bmp-binding endothelial cell precursor-derived regulator)-dependent signaling pathways. Her work focuses on understanding how endothelial cells respond to ligand, initiate signaling cascades and cellular events such as proliferation, migration, differentiation, angiogenesis, inflammation and atherosclerosis, and change the metabolism to satisfy their needs at different active status.

SPEAKER BIOGRAPHIES



Shaine A. Morris, M.D., M.P.H.

Pediatric Cardiologist
Texas Children's Hospital
Associate Professor of Pediatrics-Cardiology
Baylor College of Medicine

Dr. Shaine Morris is a Pediatric Cardiologist at Texas Children's Hospital in Houston, Texas and an Associate Professor in Pediatrics-Cardiology at Baylor College of Medicine. Dr. Morris received her MD from the University of Texas Southwestern Medical School in 2002. Dr. Morris specializes in cardiovascular imaging of the fetus, child, and young adult, and cardiovascular genetics. She is the Medical Director of the Fetal Cardiology Program that provides comprehensive care to families, including diagnosis, counseling, and management, from the time a fetal anomaly is suspected. She is a member of the fetal cardiac intervention team that offers in-utero procedures for specific heart conditions to try to optimize outcomes in major cardiac anomalies, especially procedures for hypoplastic left heart syndrome and related disorders. A large part of Dr. Morris' clinical practice is caring for children and young adults with Marfan syndrome and related genetic disorders, including Loeys-Dietz syndrome, familial thoracic aneurysms and dissections, vascular Ehlers-Danlos syndrome, and Turner syndrome. She serves as a Medical Director of the Cardiovascular Genetics program, which provides comprehensive diagnosis, counseling, and cardiovascular management for young people with genetic conditions and cardiovascular disease. Dr. Morris' research interests align with her clinic interests and focus primarily on improving outcomes for children with Marfan syndrome and related disorders. She specifically investigates novel imaging markers that may help better predict long term outcomes, and how to use these markers to determine early in life how to optimize care. Her primary goal is to prevent adverse outcomes in patients with aortic disease so that they can live long and healthy lives.

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13 - Blackburn, K.	27 - Toy, Y.	65 - Halas, M.	77 - Devkota, L.
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60 - Lusk, S.

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10 - Farraj, K.

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Disease Modeling

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POSTER SESSION SCHEDULE

SESSION I

10:00 – 11:00 a.m.

3	Structure activity optimization of ryanodine receptor modulators for the treatment of catecholaminergic polymorphic ventricular tachycardia
5	Shifts in glycolytic phenotype in smooth muscle cells of sporadic aortic aneurysms and acute dissections
11	Macrophages promote endothelial permeability following exposure to shear stress
16	Development of a novel bioreactor to explore the mechanobiology of endmt in the aortic valve
17	Numb family proteins in epicardium regulate epicardial cells differentiation and ventricular patterning during development
18	Optimizing hydrogel fabrication for aortic valve replacements: a study on ultraviolet light exposure
19	Novel quantitative approach for dynamic volumetric blood flow analysis and early embryonic cardiovascular phenotyping
21	Optogenetics as a tool for embryonic cardiovascular research
28	Long-term efficacy and safety of cardiac genome editing for catecholaminergic polymorphic ventricular tachycardia
31	Co-culture models: 3D scaffolds and their disease modeling applications
37	A novel gene therapy CM-YAPon provides long-term protection against myocardial infarction
40	Loss of pericentrin gene (pcnt) in smooth muscle cells leads to atherosclerosis
44	Critical role of endothelial injury in the initiation of aortic dissection
45	Heart failure and atrial fibrillation development in a new transverse aortic constriction mouse model (mTAC)
50	Novel REV-ERB specific agonist improves left ventricular dysfunction after pressure overload via transcription repression
51	DNA double-stranded breaks, a hallmark of aging, defined at the nucleotide resolution, are increased and associated with transcription in the cardiac myocyte genome in lmna-cardiomyopathy
52	The expression profile of proteoglycans in ascending thoracic aortic aneurysm and dissection: insights from single cell transcriptome analysis of human and mouse aortas
54	Genetic deletion of histone lysine demethylase KDM5A in cardiomyocytes attenuates LMNA-associated dilated cardiomyopathy
56	CRISPR-based genomic deletions of candidate enhancer elements associated with QT interval variation
58	Massively parallel reporter assays to identify enhancer variants underlying QT interval GWAS loci
60	Potential cardiovascular mechanisms of autoresuscitation failure in Sudden Infant Death Syndrome by aberrant NA or 5-HT function
68	Evaluation of prognostic factors for mechanical circulatory support using the Impella device among patients with cardiogenic shock from myocardial infarction
71	β 1 integrins regulate cellular behavior and cardiomyocyte organization during ventricular wall formation
72	Canonical and noncanonical heat shock factor 1 (HSF1) signaling drive atherosclerosis
74	Epigenetic regulation of adaptive genes mediated by TGF-beta and MEF2C in VSMCs during aortic disease progression
76	Activation of a GPCR, ORL1 receptor: a novel therapy to prevent heart failure progression

POSTER SESSION SCHEDULE

SESSION II

noon – 1:30 p.m.

2	The loss of striated muscle preferentially expressed gene (SPEG) kinase, leads to decreased contractility and in-creased hypertrophy in the heart leading to heart failure
4	Unraveling the behavioral phenotype of TANGO2 deficiency: lessons from transgenic mice and vitamin B deficiency
6	Folate reduces the incidence of ventricular arrhythmias in TANGO2 KO mice
9	Modified mRNAs of SRF and YAP1 attenuate apoptosis in cardiomyocytes
12	Pharmacological or genetic inhibition of LTCC promotes cardiomyocyte proliferation through inhibition of calcineurin activity
20	Nutritional vitamin supplementation is an alternative antiarrhythmic approach to prevent and treat lethal TANGO2 deficiency disorder related ventricular arrhythmias during inpatient admission
23	Mechanisms underlying dilated cardiomyopathy associated with FKBP12 deficiency
25	AKAP12 interacts with phosphodiesterase 8A (PDE8A) and β -adrenergic receptors (ADRBs) in cardiomyocytes
27	A multicenter randomized controlled trial of exercise in aortic dissection survivors
30	Characterization of singular and collective cell response to changes in distal mechanical environment
32	Sex-specific response to glutathione precursors in the old mouse heart
33	LncRNA Circa protects against post-myocardial infarction remodeling by regulating hnRNPA1 function in the heart
34	Modeling TANGO2-deficiency disorder with iPSC-CMs revealed possible Nav1.5 dysfunction
36	YAP induces a neonatal like pro-renewal niche in the adult heart
42	YAP rejuvenates cardiomyocytes by remodeling mitochondrial substrate utilization
46	CD36-retinoic acid-FABP5-PPAR δ signaling axis modulates cardiomyocytes' ability to proliferate in neonatal mice
47	TFAM drives compensatory induction of nuclear-encoded mitochondrial genes
49	YAP defines metabolic microenvironment to drive cardiac fibrosis
55	TANGO2 deficiency affects lipid metabolism in cardiac myocytes
63	Evaluating the associations between medications and aortic growth in children with bicuspid aortic valve
65	Contemporary experience with the use or repair of homograft roots in 130 proximal aortic repairs
66	Reoperation after prior aortic root replacement: evolution of technique over 30 years
70	Bone morphogenetic protein-binding endothelial regulator regulates lipolysis
73	Evaluation of large animal models with HFpEF through echocardiography
75	Non-canonical splice variants in genes for thoracic aortic disease are enriched in acute thoracic aortic dissection cases and marfan syndrome families with negative panel testing
78	Role of junctophilin-2 (JPH2) in regulating mitochondrial function and oxidative stress in cardiomyopathy

POSTER SESSION SCHEDULE

SESSION III

2:30 – 3:15 p.m.

1	IL-6 mediated STAT3 activation drives camkii activity in postoperative atrial fibrillation
7	Macrophage-mediated interleukin-6 signaling drives ryanodine receptor-2 calcium leak in postoperative atrial fibrillation
8	Atrial proteomic profiling reveals a switch towards profibrotic gene expression program in CREM-IbΔC-X mice with persistent atrial fibrillation
10	Heart slice-based bioreactor co-culture system to study cardio-oncology
13	Using preoperative characteristics to estimate patient risk of persistent paraplegia in those receiving an elective, open thoracoabdominal aortic aneurysm repair
14	Outcomes of thoracoabdominal aortic aneurysm repair in patients with and without peripheral vascular disease
15	Cycles of energy transfer in the heart — a holistic concept applied to heart failure
22	Studies of linkage and polygenic risk to improve genetic testing for cardiovascular disease across populations
24	A population-based study of aortic dissection among children and young adults, 2004–2019
26	Whole exome sequencing uncovers the genetic complexity of bicuspid aortic valve in families with early onset complications
29	Effects of glycocalyx maturity on aortic endothelial cell's response to shear stress
35	Left-right differences in Wnt inhibition underlie a pro-fibrotic microenvironment and atrial fibrillation pre-disposition for Pitx2 Deficiency
38	Gasdermin D promotes atrial arrhythmogenesis via pyroptosis-independent mechanisms
39	A novel LMNA mutant (R225X) leads to cardiac conduction disorders
41	SPEG mediates increased atrial fibrillation incidence in chronic kidney disease
43	Genome-wide profiling of TOP2B binding in human cardiomyocytes to understand doxorubicin-induced cardiotoxicity
48	A novel technique for the implantation of a wireless telemetry device in a porcine model as a valuable tool in cardiovascular research
53	Numb Family Proteins regulate left ventricular compaction by modulating autophagic process
57	CRISPR-based genomic deletions of candidate enhancer elements associated with QT interval variation
59	Automated respiratory and cardiovascular data pipeline for waveform characteristic analysis
61	Altered blood-brain barrier and platelet dynamics in the uninjured contralateral cortex following traumatic brain injury in mice
62	Clonal hematopoiesis in TET2 and ASXL1 is associated with atrial fibrillation
64	Cardiac pulmonary nerve stimulation: a single-center experience
67	Utilizing hyperoxygenated blood during left heart bypass for thoracoabdominal aortic aneurysm repairs to reduce postoperative renal dysfunction
69	A case of short QT syndrome in an adolescent male
77	Nanoparticle contrast-enhanced computed tomography in a BAPN-induced mouse model of aortic aneurysm and dissection

ABSTRACTS

Poster Number 1
Undergraduate
Arrhythmias and Channelopathies

IL-6 MEDIATED STAT3 ACTIVATION DRIVES CAMKII ACTIVITY IN POSTOPERATIVE ATRIAL FIBRILLATION

Isabelle M Ong¹, Joshua A Keefe¹, Xander HT Wehrens¹

¹Integrative Physiology, Baylor College of Medicine, Houston, TX

Background: Background: Postoperative atrial fibrillation (POAF) is AF that occurs days after cardiac surgery in 1/3 of patients and increases the risk of recurrent AF by 8-fold. The risk of POAF correlates with the degree of post-surgical inflammation, making interleukin-6 (IL-6), an inflammatory marker upregulated in POAF patients, a molecule of interest. In POAF, IL-6 activates the transcription factor STAT3 upon binding to IL-6R α and gp130. Prior studies have demonstrated that IL-6 is sufficient to induce Ca²⁺ mishandling, characterized by a sterile pericarditis rat model of POAF. Importantly, IL-6 mediated STAT3 has been demonstrated to upregulate CAMK2D transcription in human umbilical vein endothelial cell culture. We thus hypothesize that IL-6 mediated STAT3 activation leads to Ca²⁺ mishandling through CaMKII-mediated hyperphosphorylation of RyR2, a key Ca²⁺ channel, leading to POAF.

Materials/Methods: Methods: To test whether the same occurs in the heart, whole atria harvested from WT mice were treated with 50 mg/kg of IL-6 once a day for three days. Suppressor of cytokine signaling 3 (Socs3), a proxy for STAT3 pathway activation, and Camk2 δ expression were assessed by RT-qPCR. To assess the direct consequences of IL-6 on cardiomyocytes, atrial cardiomyocytes (ACMs) were isolated from WT mice and incubated with 200 ng/mL of IL-6 and 100 ng/mL of IL-6R for 30 minutes prior to imaging of RyR2 Ca²⁺ activity.

Results: Results: In IL-6 versus vehicle treated mice, whole atria showed upregulated Socs3 (18.0-fold, P<0.001) and Camk2d (2.2-fold, P=0.047) expression. IL-6 treated ACMs led to 10.0-fold (P<0.001) and 3.0-fold (P=0.047) increases in Ca²⁺ spark and wave frequency, respectively, compared to vehicle, without changes in Ca²⁺ transient amplitude and sarcoplasmic reticulum Ca²⁺ load, implying that IL-6 mediated STAT3 induces Ca²⁺ mishandling via CaMKII, leading to POAF.

Conclusions: Conclusions: Altogether, these findings provide evidence that treatments targeting the IL-6-CaMKII axis can prevent POAF.

ABSTRACTS

Poster Number 2
Undergraduate Student
Heart Failure and Cardiomyopathy

THE LOSS OF STRIATED MUSCLE PREFERENTIALLY EXPRESSED GENE (SPEG) KINASE, LEADS TO DECREASED CONTRACTILITY AND INCREASED HYPERTROPHY IN THE HEART LEADING TO HEART FAILURE

Dean Barazi¹, Yuriana Aguilar-Sanchez¹, Satadru K Lahiri¹, Joshua Keefe¹, Alberto Navarro-Garcia¹, Xander HT Wehrens¹

¹Integrative Physiology, Baylor College of Medicine, Houston, TX

Background: Heart Failure (HF) affects 6.5 million people in the US. HF is characterized by decreased contractility and increased cardiac hypertrophy. The ryanodine receptor type 2 (RyR2) regulates calcium dynamics and contractility. SPEG is a kinase that regulates intracellular calcium dynamics by phosphorylating the RyR2 at S2367. However, the role of phosphorylation at S2367 in HF progression has not been assessed. We hypothesize that SPEG knockout mice (SPEG^{GcKO}) will develop increased lung edema, heart hypertrophy, and decreased contractility, all indicative of HF.

Materials/Methods: We injected SPEG^{fl/fl} mice with AAV9-TNT-Cre-mCherry to induce SPEG knockout and analyzed the phenotypic differences. Cardiac function was assessed from echocardiograms recorded at baseline and 4, 8, and 12w post-injections. SPEG protein levels were measured by Western blot (WB).

Results: To confirm mice had SPEG protein reduced, we did WBs and saw relative to WT (1 ± 0.21), both Cre injected SPEG^{fl/fl} (0.28 ± 0.08) and SPEG^{fl/fl}-S2367D mice (0.21 ± 0.04) had reduced SPEG. SPEG^{fl/fl} mice had decreased EF at 12w vs SPEG^{fl/fl}-S2367D mice (24.4 ± 1.45 vs 42.8 ± 4.48). Lastly, we harvested to confirm that mice had both increased lung edema and cardiac hypertrophy. Additionally, cell area of SPEG^{fl/fl} and SPEG^{fl/fl}-S2367D mice was increased relative to cells isolated from WT mice.

Conclusions: Our data reveal that reduced RYR2 phosphorylation at the SPEG site is critical in HF progression. Importantly, cardiac function was protected in SPEG^{GcKO} mice by mimicking the RyR2 site- specific phosphorylation at S2367 (SPEG^{GcKO}-S67D mice). In conclusion, we found that SPEG is critical for RyR2 phosphorylation at S2367 and its loss leads to HF.

ABSTRACTS

Poster Number 3
Undergraduate Student
Arrhythmias and Channelopathies

STRUCTURE ACTIVITY OPTIMIZATION OF RYANODINE RECEPTOR MODULATORS FOR THE TREATMENT OF CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Mara R Turkieltaub Paredes¹, Oliver M Moore², Martha Sibrian-Vasquez³, Yuriana Aguilar-Sanchez⁴, Tarah A Word⁴, Ni Li⁴, Christina Y Miyake⁵, Robert M Strongin³, Xander HT Wehrens⁴
¹Integrative Physiology, Baylor College of Medicine, Houston, TX; ²Neuroscience, Baylor College of Medicine; ³Chemistry, Portland State University; ⁴Integrative Physiology, Cardiovascular Research Institute; ⁵Pediatrics, Baylor College of Medicine

Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia disorder associated with potentially lethal arrhythmias. Most CPVT cases are caused by inherited variants in the ryanodine receptor type-2 (RYR2) gene.

Materials/Methods: We synthesized >200 tetracaine derivatives and characterized 11 of those. The effects of these compounds on Ca²⁺ handling in cardiomyocytes from R176Q/+ mice were tested using confocal microscopy. The effects of lead compound MSV1302 on arrhythmia inducibility and cardiac contractility were tested using programmed electrical stimulation and echocardiography, respectively. Plasma and microsomal stability and cytotoxicity assays were also performed.

Results: Ca²⁺ imaging revealed that 4 of 11 compounds suppressed sarcoplasmic reticulum Ca²⁺ leak through mutant RyR2. Two compounds selected for further testing exhibited an EC₅₀ of 146 nM (MSV1302) and 49 nM (MSV1406), respectively. While neither compound altered baseline ECG intervals, only MSV1302 suppressed stress- and pacing-induced ventricular tachycardia in vivo in R176Q/+ mice. Echocardiography revealed that the lead compound MSV1302 did not negatively impact cardiac inotropy and chronotropy. Finally, compound MSV1302 exhibited excellent stability in plasma and microsomes and was not cytotoxic.

Conclusions: Structure activity relationship studies of second-generation tetracaine derivatives identified lead compound MSV1302 with a favorable pharmacokinetic profile. MSV1302 normalized aberrant RyR2 activity in vitro and in vivo, without altering cardiac inotropy or chronotropy. This compound may be a strong candidate for future clinical studies to determine its efficacy in CPVT patients.

ABSTRACTS

Poster Number 4
Undergraduate Student
Arrhythmias and Channelopathies

UNRAVELING THE BEHAVIORAL PHENOTYPE OF TANGO2 DEFICIENCY: LESSONS FROM TRANSGENIC MICE AND VITAMIN B DEFICIENCY

Jernie Rae Rideb¹, Andrea Wilderman¹, Yuanbiao Zhao¹, Weiyi Xu¹, Lei Qi¹, Lilei Zhang¹
¹Molecular and Human Genetics, Baylor College of Medicine

Background: TANGO2 deficiency disorder (TDD) is a rare autosomal recessive condition characterized by a spectrum of clinical manifestations, including life-threatening acute metabolic crises, muscle weakness, and cardiac arrhythmias. Neurological symptoms, such as developmental delays and ataxia, further contribute to the significant impact of TDD on patients' quality of life. Despite these clinical observations, the neurodevelopmental aspects of TDD remain poorly characterized in vivo.

Materials/Methods: To address this gap, we utilized transgenic mice with a knockout in the TANGO2 gene and conducted a comprehensive battery of behavioral assays. Through the rotating rod, catwalk, conditioned fear, parallel rod foot slip, and open field assays, we assessed various aspects of gait parameters, motor coordination, and exploratory behavior in TANGO2 knockout mice compared to wild-type.

Results: Furthermore, wild-type and knockout mice were subjected to a vitamin B-deficient diet to assess its impact on behavioral phenotypes. Previous studies have shown potential roles for vitamin B, including folate and pantothenic acid, in rescuing defects associated with TANGO2 deficiency. Given the metabolic defects observed in TDD, we hypothesized that a vitamin B-deficient diet might exacerbate the neurological phenotype in TANGO2 knockout mice, similar to the disease profile of patients.

Conclusions: Our results revealed a significant difference between TANGO2 knockout mice and wild-type controls in the rotating rod assay, indicating impaired motor coordination in knockout mice on a chow diet. Furthermore, alterations in gait patterns were observed in TANGO2 knockout mice compared to controls in the catwalk assay. Importantly, vitamin B deficiency exacerbated these differences, suggesting a potential interaction between TANGO2 deficiency and vitamin B. Ongoing investigations will explore the potential therapeutic benefits of vitamin B5 supplementation in rescuing these behavioral abnormalities.

ABSTRACTS

Poster Number 5
Graduate Student
Aortopathy and Valvular Heart Disease

SHIFTS IN GLYCOLYTIC PHENOTYPE IN SMOOTH MUSCLE CELLS OF SPORADIC AORTIC ANEURYSMS AND ACUTE DISSECTIONS

Samantha Xu¹, Yanming Li¹, Chen Zhang¹, Hernan G Vasquez¹, Robert Seniors¹, Kimberly R Rebello¹, Joseph S Coselli¹, Hong S Lu², Alan Daugherty², Dianna Milewicz³, Scott A LeMaire⁴, Ying H Shen¹

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Background: Ascending thoracic aortic aneurysms (ATAA) and acute dissections (ATAD) are associated with high risk of mortality. We investigated the transcriptomic profile of glycolysis in smooth muscle cells (SMCs) in human aortic tissue and its potential involvement in promoting an inflammatory phenotype in SMCs of sporadic ATAA and ATAD. We hypothesized that glycolytic activity in SMCs is elevated in both ATAA and ATAD compared to healthy aortas, and that this effect is mediated by the STING-IRF3 pro-inflammatory signaling pathway.

Materials/Methods: We performed single cell RNA sequencing (scRNA-seq) analysis of ascending aortic tissue from 9 patients with ATAA without dissection, 9 patients with ATAD, and 8 organ donor control subjects. Single-cell assay for transposase accessible chromatin using sequencing (scATAC-seq) and scRNA-seq analyses were performed in ascending aortic tissues from wild-type (WT) mice infused with angiotensin II (Ang II), WT mice infused with saline (control), and Sting^{-/-} mice infused with Ang II.

Results: In human aortic tissues, glycolytic genes (e.g., HK1, LDHA) and predicted glycolytic activity in SMCs were progressively upregulated from control to ATAA to ATAD, especially in inflammatory SMCs. In Ang II-infused mice, scATAC-seq analyses revealed higher gene activity of glycolysis genes in inflammatory SMCs of Ang II-infused mice. Chromatin accessibility of glycolytic genes in SMCs was elevated compared to controls, suggesting potential epigenetic regulation by chromatin remodeling.

Furthermore, the activity of most glycolytic genes were positively associated with the motif activity of Irf3, which is increased in the Ang II-infused mice. Finally, Sting deficiency partially prevented Ang II-induced upregulation of glycolytic genes in SMCs.

Conclusions: Glycolytic gene expression in SMCs are progressively increased from control to ATAA to ATAD. Activation of STING-IRF3 proinflammatory signaling may play a critical role in the epigenetic induction of glycolytic genes.

ABSTRACTS

Poster Number 6
Graduate Student
Arrhythmias and Channelopathies

FOLATE REDUCES THE INCIDENCE OF VENTRICULAR ARRHYTHMIAS IN TANGO2 KO MICE

William Whitfield¹, Maria J Arredondo Sancristobal¹, Na Li¹

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Background: TANGO2 deficiency disorder (TDD), identified in 2016, affects more than 8,000 individuals worldwide. One of its defining traits is the susceptibility to develop QTc prolongation and life-threatening ventricular tachycardia (VT). Recent clinical findings have indicated that multivitamins can prevent VT in TDD, particularly those within the B-complex. Intriguingly, individuals who solely consumed folate (B9) demonstrated similar positive outcomes. Our study aimed to investigate the efficacy and mechanisms involved in B9 supplementation as a rescue intervention for VT in TANGO2 ^{-/-} mice.

Materials/Methods: A TANGO2 KO strain was acquired from Knockout Mouse Project at Baylor College of Medicine. Two cohorts, each of 10-week-old wildtype (WT) and TANGO2 ^{-/-} mice, were subjected to a vitamin B-complex deficiency diet (VBD) for 5 days. Additionally, one of the groups received B9 supplementation via drinking water. After this period, we conducted echocardiography and electrophysiology studies involving electrical stimulation to evaluate the inducibility of VT and cardiac function.

Results: While no pacing-induced VT was observed in WT or TANGO2 ^{-/-} mice on a regular diet, TANGO2^{-/-} mice on VBD exhibited an increased incidence of pacing-induced VT compared to WT mice. However, the incidence of pacing-induced VT was significantly reduced in the TANGO2^{-/-} mice on VBD supplemented with folate compared to TANGO2^{-/-} mice on VBD alone. QTc was significantly prolonged compared with the WT on VBD, and B9 supplementation did not change this outcome. Echocardiography and histology studies revealed no significant differences in ventricular structure or contractility between WT and TANGO2^{-/-} mice, regardless of the diet.

Conclusions: It is imperative to identify novel therapeutic targets to prevent the associated mortality of TDD VT. These findings suggest a potential therapeutic value of B9 supplementation in mitigating VT susceptibility associated with TDD and warrant further investigation into its underlying mechanisms.

ABSTRACTS

Poster Number 7
Graduate Student
Arrhythmias and Channelopathies

MACROPHAGE-MEDIATED INTERLEUKIN-6 SIGNALING DRIVES RYANODINE RECEPTOR-2 CALCIUM LEAK IN POSTOPERATIVE ATRIAL FIBRILLATION

Joshua A Keefe¹, Yuriana Aguilar-Sanchez¹, Isabelle Ong¹, Alberto Navarro-Garcia¹, Amelie Pasche², Issam Abu-Taha³, Marcel Tekook³, Florian Bruns³, Dean Barazi¹, Markus Kamler⁴, Ying Shen⁵, Dobromir Dobrev³, Xander HT Wehrens¹

¹Integrative Physiology, Baylor College of Medicine; ²Department of Cardiology, Angiology and Pneumology, University Hospital Heidelberg; ³Institute of Pharmacology, University Duisburg-Essen; ⁴Department of Thoracic and Cardiovascular Surgery, University Hospital Essen; ⁵Department of Surgery, Division of Cardiothoracic Surgery, Baylor College of Medicine

Background: Postoperative atrial fibrillation (poAF) is self-limited AF that occurs days after cardiac surgery in one-third of patients. The degree of perioperative increase in systemic inflammation, particularly involving interleukin (IL)-6, correlates with poAF risk. However, no studies to-date have identified the cell types involved nor mechanistically linked IL-6 signaling to arrhythmia mechanisms.

Materials/Methods: We performed single-cell RNA sequencing (scRNAseq), followed by pseudotime trajectory analyses comparing atrial non-myocytes from mice with versus without poAF. We followed up our scRNAseq findings with pharmacologic and genetic approaches in mice to validate pathways related to macrophage-mediated IL-6 signaling. We used confocal imaging to assess calcium-signaling mechanisms at the single atrial cardiomyocyte (ACM) level.

Results: Our scRNAseq results demonstrated macrophages to be the most prominently altered atrial cell type. Pseudotime trajectory analyses revealed IL-6 to be the top cytokine altered in macrophages, which we confirmed by western blot demonstrating a 1.7-fold ($P=0.012$) increase in atrial IL-6 protein in mice with versus without poAF. Indeed, both macrophage depletion and macrophage-specific Il-6ra conditional knockout decreased poAF inducibility by 5.2-fold ($P=0.048$) and 5.5-fold ($P=0.027$) respectively. Downstream inhibition using an FDA-approved STAT3 inhibitor also decreased poAF incidence (6-fold decrease, $P=0.022$). At the single ACM level, IL-6 challenge led to a 4.5-fold ($P=0.002$) increase in arrhythmogenic calcium (Ca^{2+}) sparks that was rescued by CaMKII inhibition.

Conclusions: Altogether, we integrate biochemical, functional, and single-cell sequencing data to demonstrate that IL-6Ra from macrophages is required for arrhythmogenic RyR2 dysfunction in poAF. Our findings portend significant therapeutic utility by providing mechanistic evidence that targeting the IL-6 axis may be used for poAF prevention in a clinically amenable timeframe.

ABSTRACTS

Poster Number 8
Graduate Student
Arrhythmias and Channelopathies

ATRIAL PROTEOMIC PROFILING REVEALS A SWITCH TOWARDS PROFIBROTIC GENE EXPRESSION PROGRAM IN CREM-IBΔC-X MICE WITH PERSISTENT ATRIAL FIBRILLATION

Shuai Zhao¹, Mohit Hulsurkar¹, Xander HT Wehrens¹
¹Integrative Physiology, Baylor College of Medicine

Background: Overexpression of the CREM (cAMP response element-binding modulator) isoform CREM-IbΔC-X in transgenic mice (CREM-Tg) causes the age-dependent development of spontaneous AF. We aim to identify key proteome signatures and biological processes accompanying the development of persistent AF through integrated proteomics and bioinformatics analysis.

Materials/Methods: Atrial tissue samples from three CREM-Tg mice and three wild-type littermates were subjected to unbiased mass spectrometry-based quantitative proteomics, differential expression and pathway enrichment analysis, and protein-protein interaction (PPI) network analysis.

Results: A total of 98 differentially expressed proteins were identified. Gene ontology analysis revealed enrichment for biological processes regulating actin cytoskeleton organization and extracellular matrix (ECM) dynamics. Changes in ITGAV, FBLN5, and LCP1 were identified as being relevant to atrial fibrosis and remodeling based on expression changes, co-expression patterns, and PPI network analysis. Comparative analysis with previously published datasets revealed a shift in protein expression patterns from ion-channel and metabolic regulators in young CREM-Tg mice to profibrotic remodeling factors in older CREM-Tg mice. Furthermore, older CREM-Tg mice exhibited protein expression patterns reminiscent of those seen in humans with persistent AF.

Conclusions: This study uncovered distinct temporal changes in atrial protein expression patterns with age in CREM-Tg mice consistent with the progressive evolution of AF. Future studies into the role of the key differentially abundant proteins identified in this study in AF progression may open new therapeutic avenues to control atrial fibrosis and substrate development in AF.

ABSTRACTS

Poster Number 9
Graduate Student
Cardiac Regeneration and Stem Cells

MODIFIED MRNAS OF SRF AND YAP1 ATTENUATE APOPTOSIS IN CARDIOMYOCYTES

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Background: The ability of the heart to regenerate cardiomyocytes is impaired after it exits the early cell cycle and putative proliferative stages (Ye et al., 2018; Zhu et al., 2018). This inability of the heart to significantly regenerate cardiomyocytes (after terminal differentiation) constitutes a major challenge, as it is unable to initiate and achieve ample repair mechanisms after injuries including those caused by myocardial infarction. Usually, myocardial infarction leads to the accumulation of fibrotic scar tissue, and subsequent loss of functional cardiomyocytes, regular cardiac function, and ultimately, heart failure (Bergmann et al., 2015). Heart failure features prominently in heart disease, which is a leading cause of mortality and morbidity in humans globally. Two factors, SRF - serum response factor and YAP1 - yes associated protein 1, have been shown to be very important in heart development. Modified mRNAs (mmRNA) coding for a mutant SRF and YAP1 have been shown to initiate regenerative, repair and pro-survival signals in cardiomyocytes (Xiao et al, 2022), with concurrent upregulation of intracellular and exosomal miRNAs. This research investigated and characterized these miRNA and showed how they contribute to the survival of cardiomyocytes especially via the inhibition programmed cell death. We hypothesized that the mmRNAs of SRF and YAP1 upregulate the expression of miRNAs, which act within the cells and on adjacent ones to downregulate several apoptotic factors via RNA-interference.

Materials/Methods: Experiments and assays include RNA-sequencing, immunofluorescence, immunohistochemistry, flow cytometry and exosome profiling.

Results: Individual apoptotic markers were downregulated significantly, leading to the wholesale inhibition of apoptosis and, consequently, the viability of cardiomyocytes.

Conclusions: We conclude that mmRNA of SRF and YAP1 upregulate the expression of intracellular and exosomal miRNAs which inhibit apoptosis and promote the survival of cardiomyocytes by RNA interference.

ABSTRACTS

Poster Number 10
Graduate Student
Technology Development

HEART SLICE-BASED BIOREACTOR CO-CULTURE SYSTEM TO STUDY CARDIO-ONCOLOGY

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Background: Recent studies have shown a possible crosstalk between cardiovascular disease (CVD) and the progression of cancer. This has led to the establishment of a new research field called cardio- oncology which aims to understand the bi-directional relationship between CVD and cancer progression.

Materials/Methods: Here, we aim to develop a bioreactor co-culture platform that incorporates cardiac tissue slices and cancer cells to investigate this possible crosstalk. Our lab recently developed a cardiac tissue culture model (CTCM) that can emulate the cardiac cycle by subjecting 300µm thick heart slices to dynamic mechanical loading with synchronized electrical stimulation. The CTCM system can fully maintain tissue slices for 12 days. Additionally, by controlling the hemodynamic pressures, the CTCM can emulate various CVDs, such as over-stretch-induced cardiac hypertrophy. Using the CTCM design, a co-culture bioreactor system was designed to allow continuous fluid exchange between cardiac tissue slices and other cultured cell lines. This bioreactor consists of the CTCM device, a customized 3-well culture chamber, a media reservoir, and a peristaltic pump, all connected by flexible silicone tubing with one-directional valves.

Results: Using SolidWorks FloXpress CFD software and dual-dye perfusion analysis, the flow distribution within the CTCM culture chamber was characterized and optimized to allow a uniform fluid exchange across all tissue slices.

Conclusions: Overall, a CTCM co-culture bioreactor system was designed to be used as a platform to investigate the crosstalk between CVD-induced cardiac tissue and cancer progression. This bioreactor has the potential to be used for studying other multiorgan crosstalks such as brain-heart, liver-heart, and kidney-heart.

ABSTRACTS

Poster Number 11
Graduate Student
Congenital Developmental Heart Disease

MACROPHAGES PROMOTE ENDOTHELIAL PERMEABILITY FOLLOWING EXPOSURE TO SHEAR STRESS

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Background: Discrete subaortic stenosis (DSS) is a pediatric cardiovascular disease distinguished by fibrotic growth within the left ventricular outflow tract (LVOT) resulting in elevated flow and shear stress. Surgical resection of the growth poses challenges with a recurrence rate of 20-30%. After the surgical removal of the fibrotic growth, macrophages are exposed to pathological shear stress, yet the consequences of this exposure remain largely unexplored. We hypothesize that the pathological shear stress characteristic of DSS induces macrophages to release pro-inflammatory cytokines, leading to increased endothelial permeability, infiltration of monocytes, and promotion of fibrosis.

Materials/Methods: Human monocytes were isolated from donor buffy coats and subsequently differentiated into monocyte-derived macrophages (MDMs). MDMs and human aortic endothelial cells (HAECs) were then subjected to varying levels of shear: static, 15 dynes/cm² (physiological), or 35 dynes/cm² (pathological) for 3 or 24 hours. Conditioned media (CM) from MDMs was collected, analyzed using a Luminex system, and added to HAECs. HAECs were then analyzed for changes in gene expression and permeability.

Results: MDMs exposed to shear stress secreted pro-inflammatory cytokines such as TNF- α and IL-8. HAECs exposed to shear stress had decreased inflammatory gene expression of VCAM and E-selectin, but had increased expression after exposure to MDM CM. Immunofluorescent staining of VE-Cadherin showed less expression in HAECs exposed to CM compared to HAECs exposed to direct shear, indicating increased permeability after exposure to CM. These results were further confirmed using a permeability assay.

Conclusions: MDMs exposed to shear stress could directly contribute to endothelial permeability, allowing for invasion of monocytes, differentiation into macrophages, and the propagation of fibrosis. Understanding these mechanisms could open new avenues for therapeutic strategies, aiming not only to treat DSS but also prevent its recurrence.

ABSTRACTS

Poster Number 12
Graduate Student
Cardiac Regeneration and Stem Cells

PHARMACOLOGICAL OR GENETIC INHIBITION OF LTCC PROMOTES CARDIOMYOCYTE PROLIFERATION THROUGH INHIBITION OF CALCINEURIN ACTIVITY

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Background: Cardiomyocytes (CMs) lost during ischemic cardiac injury cannot be replaced due to their limited proliferative capacity, which leads to progressive heart failure. Calcium (Ca²⁺) is an important signal transducer that regulates key cellular processes, but its role in regulating CM proliferation is incompletely understood.

Materials/Methods: We performed a drug screening targeting proteins involved in CM calcium cycling in human iPS-derived cardiac organoids. Ki-67 and PHH3 expression was assessed as an S-G2/M phase marker. MADM mice was used to assess proliferation in vivo.

Results: The screening revealed that only the inhibition of L-Type Calcium Channel (LTCC), but not other Ca²⁺ regulatory proteins (SERCA or RYR), induced the CM cell cycle. To confirm this finding, we overexpressed Ras-Related Associated with Diabetes (RRAD), an endogenous regulator of LTCC activity. RRAD overexpression significantly reduced the intracellular calcium amplitude. RRAD overexpression promoted cell cycle induction, increased CM number, and upregulated cell cycle genes in primary neonatal CMs, human heart slices, human iPS-derived cardiac organoids, and in vivo using MADM mice. Moreover, RRAD overexpression significantly augmented the CM response to other cell cycle stimulators such as Cyclin A2, a combination of CDK4 and cyclin D (2F), or a combination of CDK1, CDK4, cyclin D, and cyclin B (4F). Mechanistically, we found that RRAD overexpression reduced the activity of Ca²⁺ dependent serine/threonine phosphatase (Calcineurin), as indicated by a significant reduction in calcineurin phosphatase activity in vitro and the expression levels of the calcineurin downstream effectors such as Rcan1 expression as well as translocation of Hoxb13 to the CM nucleus.

Conclusions: Pharmacological or genetic inhibition of LTCC promotes cell cycle induction in CMs through modulation of calcineurin activity. Further work in vivo is needed to test whether RRAD overexpression could improve cardiac function after ischemic injury.

ABSTRACTS

Poster Number 13
Graduate Student
Aortopathy and Valvular Heart Disease

USING PREOPERATIVE CHARACTERISTICS TO ESTIMATE PATIENT RISK OF PERSISTENT PARAPLEGIA IN THOSE RECEIVING AN ELECTIVE, OPEN THORACOABDOMINAL AORTIC ANEURYSM REPAIR

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Background: Spinal cord injury is a significant concern for patients undergoing thoracoabdominal aortic aneurysm repair (TAAAR)—the most substantial of which is persistent paraplegia. For patients considering an elective, open TAAAR, it is vital to properly estimate patient-level complication risk. We hypothesize that we can accurately estimate risk of persistent paraplegia in TAAAR repairs using preoperative factors.

Materials/Methods: Data from 2,640 patients undergoing an open, elective TAAAR between the years 1986-2024 from a single practice were analyzed. The two comparison cohorts were patients who did not have any post-operative spinal cord deficit and those with persistent paraplegia (paralysis of lower limbs)—patients with a temporary spinal cord deficit or persistent paraparesis (e.g. leg weakness) were excluded. A complication was considered persistent if it was present at the time of discharge or death. 4 predictive models were evaluated: multivariable logistic regression (MLR), random forests (RF), support vector machines (SVM), and gradient boosting machines (GBM). The predictive effectiveness of each were compared based on the test C-statistic (C) from an 80:20, 1000 iteration cross validation scheme. The MLR model was also converted into a nomogram to aid in patient counseling.

Results: 2.6% of patients had persistent paraplegia. Of the 4 models, the GBM was the most effective (C=0.79 [0.75, 0.81]; median [Q1, Q2]), with the MLR model being close behind (0.78 [0.74, 0.81]). The final MLR model included 6 predictors: diabetes (OR=2.48, P=.009), history of percutaneous coronary intervention or stent (3.04, <.001), chronic kidney disease (2.48, <.001), history of tobacco use (13.25, .01), a symptomatic aorta (1.96, .01), and the Crawford Extent of repair (II: 4.00, <.001; III: 2.80, .02; IV: 2.14, .06).

Conclusions: Based on preoperative characteristics, the risk of persistent paraplegia can be accurately estimated for patients undergoing an elective, open TAAAR.

ABSTRACTS

Poster Number 14
Graduate Student
Aortopathy and Valvular Heart Disease

OUTCOMES OF THORACOABDOMINAL AORTIC ANEURYSM REPAIR IN PATIENTS WITH AND WITHOUT PERIPHERAL VASCULAR DISEASE

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Background: Peripheral vascular disease (PVD) is associated with other atherosclerotic diseases that are common in patients with thoracoabdominal aortic aneurysms (TAAA); however, its association with TAAA repair is not well studied. This study aims to investigate the relationship between PVD and outcomes of TAAA repair.

Materials/Methods: This retrospective, single-practice study analyzed 3,772 patients who had a TAAA repair from 1990-2023. Included were 891 (23.6%) patients with PVD and 2,881 (76.4%) patients without PVD. Preoperative, perioperative, and postoperative factors were compared. Adverse events included operative mortality (within 30 days of discharge or hospital transfer) or persistent (ie, present at discharge or at time of death) stroke, paraplegia, paraparesis, or renal failure requiring dialysis.

Results: The median age of patients with PVD was 69 [64-75], and without PVD was 66 [56-73]. Patients without PVD were more likely to have a heritable aortic disorder (12.9 % vs 4.0%, $P<.001$). Patients with PVD and without PVD more often underwent extent IV repair and extent I repair, respectively (30.4% vs 16.8%, $P<.001$; 29.4% vs 16.9%, $P<.001$). Management of visceral arteries by endarterectomy, stenting, or bypass was required more often in PVD patients (55.8% vs 40.1%, $P<.001$). There was no difference in operative mortality between patients with and without PVD (9.2% vs 8.4%, $P=.5$). Adverse events were increased in PVD patients (17.6% vs 14.4%, $P=.02$), specifically persistent stroke (3.6% vs 2.0%, $P=.009$). Spinal cord deficit occurred more often in PVD patients (12.3% vs 9.1%, $P=.004$); however, much was transient with no significant difference in the incidence of persistent paraplegia between groups (3.6% vs 2.7%, $P=.2$).

Conclusions: Our data suggest that PVD is associated with significant postoperative differences after TAAA repair. PVD was associated with higher rates of adverse events after TAAA repair, including a higher rate of persistent stroke, which may necessitate careful monitoring after repair.

ABSTRACTS

Poster Number 15
Graduate Student
Heart Failure and Cardiomyopathy

CYCLES OF ENERGY TRANSFER IN THE HEART – A HOLISTIC CONCEPT APPLIED TO HEART FAILURE

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Background: Cardiomyocytes in heart failure display a characteristic shift in their metabolism, and numerous efforts have attempted to target specific metabolic cycles and replenish their metabolites. We previously proposed a model of heart failure comprised of six interconnected cycles based on these endeavors: the circulation, the Krebs cycle, the NAD⁺/NADH cycle, generation of the proton gradient across the inner mitochondrial membrane, the ATP/ADP cycle, and Ca²⁺-dependent cross-bridge cycling.

Materials/Methods: Considering a recent resurgence to augment oxygen availability in heart failure through interventions such as iron supplementation and liberal blood transfusions, we aimed to amend our model to contextualize these modalities in terms of moiety conservation. Using published research in both human and murine models, we argue these strategies restore an additional cycle of energy transfer through enhancing mitochondrial pyruvate carrier (MPC) expression and pyruvate anaplerosis.

Results: Metabolomic data from published studies in heart failure reveal elevated pyruvate with a concomitant decrease in Krebs cycle intermediates. Additionally, MPC is downregulated in both heart failure and hypoxic conditions, with increased expression upon mechanical unloading with left ventricular assist device implantation. MPC-deficiency alters expression of enzymes involved in pyruvate carboxylation and decarboxylation, increases intermediates of biosynthetic pathways, and eventually precipitates cardiac hypertrophy and dilated cardiomyopathy.

Conclusions: Collectively, we propose an amended model of energy transfer in heart failure and argue oxygen availability and anaplerosis of pyruvate to be a necessary target of restoring cardiac function.

ABSTRACTS

Poster Number 16
Graduate Student
Congenital Development Disease

DEVELOPMENT OF A NOVEL BIOREACTOR TO EXPLORE THE MECHANOBIOLOGY OF ENDMT IN THE AORTIC VALVE

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Background: Bicuspid aortic valve disease (BAV) is the most common sexually dimorphic congenital heart deformation, affecting 1.5% of 46,XY men and 0.5% of 46,XX women. In this condition, the aortic valve is underdeveloped with only two cusps, increasing the probability for early onset of aortic valve disease. It is theorized that non-syndromic BAV cases are caused by mutations that impair a conserved phenotypic regulatory pathway called endothelial-mesenchymal transition (endMT), a mechanism of cellular plasticity that allows endothelial cells to lose their polarity and cell-cell adhesion, restructure their cytoskeleton and become invasive. EndMT has been observed to be critical for physiological heart septation, theorized to have a role in BAV and reported to be regulated by microenvironmental factors such as substrate stiffness, composition, and disturbed flow. The influence of these factors on endMT has been proven through various techniques but have not been fully explored pertinent to the endocardial cushions - embryonic tissues that mature into the aortic valve.

Materials/Methods: To recapitulate this microenvironment, we are integrating (1) hydrogel scaffolds into a cone-plate system (CVS) using (2) a recessed base that can expose (3) male and female porcine aortic valve endothelial cells to shear stress. Polyethylene glycol diacrylate scaffolds were formulated with hyaluronic acid and peptides that enable migration through matrix-metalloprotease degradation.

Results: The compressive stiffness of the fabricated scaffolds were <5 kPa and can be integrated into the CVS. Porcine aortic valve endothelial cells can be isolated through magnetic activated cell sorting to serve as a relevant cell line for tissue engineered models and study the influence of biological sex in BAV and aortic valve disease.

Conclusions: This bioreactor design will enable the scientific community to elucidate the influence of biological sex, substrate composition and stiffness in the mechanobiology of endMT in conjunction with shear stress.

ABSTRACTS

Poster Number 17
Graduate Student
Congenital Development Disease

NUMB FAMILY PROTEINS IN EPICARDIUM REGULATE EPICARDIAL CELLS DIFFERENTIATION AND VENTRICULAR PATTERNING DURING DEVELOPMENT

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Background: Numb Family Proteins (NFPs), specifically two mammalian homologs Numb (Nb) and Numbl like (Nl), have been evident to regulate essential cardiac functions during development. Previous studies reported NFPs as integral for epicardial cells (EpiCs) epithelial mesenchymal-transition (EMT). However, whether NFPs in epicardium regulate EpiCs differentiation during development have not been explored. In this study, we investigated how NFPs in epicardium regulate EpiCs EMT and differentiation into Cardiac Fibroblasts (CFs) to modulate cardiac morphogenesis and subsequently affect maintenance of adult heart.

Materials/Methods: We deleted Nb and Nl in Tbx18Cre/+ epicardium lineage and refer to this as EDKO. We harvested hearts at embryonic day 15.5/18.5 and assessed morphological and mechanistic differences between control and EDKOs. Echocardiographic techniques were used to examine adult heart structure and functions.

Results: Our findings revealed that EDKO embryonic hearts display specific morphology with extended shape of left ventricle. We found a striking difference between female and male EDKOs in terms of survival to adulthood. Reduced EpiCs EMT and CFs migration distances, and reduced expression of smooth muscle cells (SMCs) and pericytes have been observed in EDKOs. Strikingly, EDKO embryonic hearts show defects in ventricular compaction, wall patterning and in cell proliferation. Furthermore, when survived to adult stage, EDKO hearts revealed significant cardiac structural and functional changes. While digging into regulatory pathways, we found changes in Fibroblast growth factor receptor (Fgfrs)/p-Erk pathway and in activation of Notch1 in EDKO hearts.

Conclusions: NFPs in epicardium regulate EpiCs EMT to affect EpiCs differentiation into CFs and SMCs and regulate ventricular wall morphogenesis during development. It also helps maintain cardiac structure and function in their adult stages. Fgfrs and Notch1 pathway could be the possible mechanism behind cardiac morphogenetic regulation by NFPs in epicardium.

ABSTRACTS

Poster Number 18
Graduate Student
Aortopathy and Valvular Heart Disease

OPTIMIZING HYDROGEL FABRICATION FOR AORTIC VALVE REPLACEMENTS: A STUDY ON ULTRAVIOLET LIGHT EXPOSURE

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Background: Heart valve diseases represent a substantial burden in healthcare, frequently necessitating surgical interventions for treatment. Tissue engineering has emerged as a promising avenue, with hydrogels showcasing adjustable properties that hold potential as a viable alternative therapeutic strategy. Emphasizing the importance of replicating the inherent mechanical characteristics of tissues, especially in the context of aortic tissue engineering, becomes paramount for achieving favorable and successful treatment outcomes. By focusing on mimicking these natural mechanics through innovative approaches like hydrogel fabrication, researchers aim to enhance the efficacy and longevity of treatments for heart valve diseases, paving the way for more personalized and effective interventions in cardiovascular care.

Materials/Methods: This study introduces a novel method for fabricating PEGDA hydrogel composites. Initially, PEGDA polymer is dissolved in ultra-pure water with Irgacure 2959 as the photo initiator. UV crosslinking is then performed using the G171 device, providing precise control over the crosslinking process. The research aims to determine the optimal energy delivery for crosslinking while investigating the relationship between UV dosage and mechanical properties.

Results: The study successfully achieved varying degrees of crosslinking, allowing for the customization of mechanical properties. Optimal energy delivery for crosslinking was identified, and the impact of UV exposure on mechanical properties was elucidated. The experiments are still ongoing.

Conclusions: This research advances the understanding of hydrogel fabrication for cardiovascular tissue engineering, enhancing the reproducibility and efficiency of production processes. These findings contribute to the development of functional replacements for heart valve diseases, addressing a critical need in healthcare.

ABSTRACTS

Poster Number 19
Graduate Student
Congenital Developmental Heart Disease

NOVEL QUANTITATIVE APPROACH FOR DYNAMIC VOLUMETRIC BLOOD FLOW ANALYSIS AND EARLY EMBRYONIC CARDIOVASCULAR PHENOTYPING

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Background: Congenital heart defects are present in an estimated 1.8% of newborns worldwide. The biomechanical force created by early blood flow dynamics is vital to proper heart formation and development, yet spatially and temporally resolved blood flow measurements in the early embryonic heart remain challenging. This project develops a quantitative blood flow analysis approach in early embryonic mouse models using optical coherence tomography (OCT) for functional cardiodynamic phenotyping.

Materials/Methods: Structural OCT imaging was performed on cultured mouse embryos on embryonic day 8.5 (E8.5) volumetrically at 100 Hz as a single volume of 30,000 frames with ~55 frames per heartbeat. The heartbeats were aligned and regions of blood flow segmented following previously established methods. The new flow speed analysis is based on the duration each pixel detects a particle, particle size statistics, and the periodicity of the cardiac cycle. Doppler OCT in regions of defined orientation was used as calibration and validation.

Results: We track flow profiles throughout the dynamic regions of blood flow within the embryonic cardiovascular system. The characteristic pattern of blood flow speeds is demonstrated in spatially and temporally resolved signal within the embryonic heart and throughout the imaged vasculature as the heart beats.

Conclusions: We present quantitative OCT cardiodynamic techniques for direction-independent analysis of early blood flow and demonstrate this approach in a cultured E8.5 embryonic mouse. The presented method has the potential to allow biomechanical studies of blood flow during heart development and functional phenotyping over developmental milestones and in existing genetic models of congenital heart defects.

ABSTRACTS

Poster Number 20
Graduate Student
Arrhythmias and Channelopathies

NUTRITIONAL VITAMIN SUPPLEMENTATION IS AN ALTERNATIVE ANTIARRHYTHMIC APPROACH TO PREVENT AND TREAT LETHAL TANGO2 DEFICIENCY DISORDER RELATED VENTRICULAR ARRHYTHMIAS DURING INPATIENT ADMISSION

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Background: TANGO2 deficiency disorder (TDD) is associated with marked QT prolongation and torsade de pointes. Often misdiagnosed as long QT syndrome, TDD is important to recognize since VT progresses to cardiac arrest in 58% of the cases. Published data support B-vitamin supplementation (VitSupp) may prevents VT in the outpatient setting. However, for inpatient TDD admissions, VT is recalcitrant to antiarrhythmics (AA). It remains unclear why VT resolves in some but not others. We hypothesized that early and consistent VitSupp via NG-tube or TPN at or above the 100% recommended daily B-vitamin allowance (RDA100) can prevent and suppress VT in the inpatient setting.

Materials/Methods: Retrospective multicenter review of TDD inpatients during metabolic crisis who received NG-tube or TPN feeds. Timing and dose of VitSupp initiation was compared to VT initiation, termination, death, and QTc normalization. Linear regression was used to assess RDA100 and the timing of VT termination.

Results: 11 inpatient admissions (9 patients, median QTc 545msec) were analyzed (8 with VT; 3 without VT). In 3 without VT, VitSupp at RDA100 was initiated before VT occurred. VitSupp at RDA100 was associated with VT termination within 48 hours in 3 of 8 admissions with VT. In the other 5 with VT, VitSupp did not meet RDA100. The time to VT termination was longer (4-6 days), and 2 deaths were observed. In 1 outlier, VT terminated the day VitSupp was initiated although less than RDA. Although not statistically significant, each 10% increase in RDA100 trended to earlier VT termination by 6 hours (p=0.059). QTc normalized faster with TPN (2-5d) than with enteral VitSupp (9-10d). In 2 deaths, RDA100 was not met prior to death and QTc did not normalize.

Conclusions: No single AA is effective for VT treatment in TDD. Early initiation and adequate VitSupp may help suppress VT and normalize the QTc. Higher doses of RDA100 may be beneficial. Nutritional supplementation should be considered in all inpatients with TDD.

ABSTRACTS

Poster Number 21
Graduate Student
Congenital Developmental Heart Disease

OPTOGENETICS AS A TOOL FOR EMBRYONIC CARDIOVASCULAR RESEARCH

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Background: Congenital heart defects (CHD) are highly prevalent, impacting over 1% of newborns globally. To enhance diagnostics, prevention, and treatment strategies for CHD, researchers extensively utilize genetic animal models that mimic human defects, alongside to study genetic, molecular, and biomechanical factors. Within this context, optogenetics emerges as a significant technology for the non-invasive and reversible control of cardiac activity. This project investigates optogenetic control of embryonic mouse cardiodynamics and locates early pacing regions of the heart.

Materials/Methods: We generated mouse embryos that ubiquitously express the light-sensitive protein Channelrhodopsin-2 (ChR2) in all cells through CMV-cre cross. At embryonic day 8.5, these embryos were extracted and maintained live in static culture. We stimulated the cardiac cells with a 473 nm Coherent laser set to a power of 10 mW in conjunction with a Zeiss Stemi 508 bright-field microscope and imaged with a Zeiss AxioCam 506 color camera at 26 Hz. The cardiodynamics response was quantified using custom Matlab codes.

Results: Cardiac responses varied by region and intensity of the light used. Pulsed stimulation allows control of cardiodynamic pace and has a milder impact on viability, compared to continuous wave stimulation, which was advantageous for quicker mapping optogenetic responses in the heart. By using these innovative optogenetic techniques, we can now spatially map cardiac pacemaker locations within the embryonic heart. We identified pacemaker distribution during development by mapping at different stages of embryonic heart growth, specifically at the 4-5 somite, 6-7 somite, and 8-9 somite stages.

Conclusions: This research establishes cardiac optogenetics as an exciting novel tool for embryonic biomechanical studies in mice and possibly other model organisms, which could eventually lead to a better understanding of cardiogenesis and improved management of CHD.

ABSTRACTS

Poster Number 22
Graduate Student
CAD, Atherosclerosis, Ischemia

STUDIES OF LINKAGE AND POLYGENIC RISK TO IMPROVE GENETIC TESTING FOR CARDIOVASCULAR DISEASE ACROSS POPULATIONS

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Background: Genetics can influence cardiovascular disease (CVD) through blood lipids like lipoprotein A (Lp(a)). Lp(a) is strongly regulated by genetics and several variants within the gene LPA are integrated into a clinical gene panel to identify risk of CVD. However, recent findings identified poor predictive transferability to Hispanic individuals, which may be due to different patterns of genetic variation and linkage across ancestries.

Materials/Methods: To combat this, we perform ancestry-informed analyses of linkage and generate a novel polygenic scoring model accounting for both a single locus of large effect with polygenic variation. We start by investigating linkage in Latin American (LAT) and European (EUR) individuals of the 1000 Genomes Project. We also evaluated whether considering polygenic burden with a KIV-2 proxy locus would improve predictive performance across populations by building upon an Lp(a) PRS on EUR individuals of the UK Biobank with variants associating well with KIV-2 across populations.

Results: We identified a recombination event in LPA where recombination rates decreased with the proportion of EUR ancestry present in LAT individuals. This recombination event differentially disrupts linkage of a clinically used LPA variant to KIV-2, a critical repetitive locus in LPA that is infrequently called. This suggests that underperformance of current clinically tested variants in LPA in Hispanic populations may be explained by more frequent recombination events decreasing their tagging of KIV-2. In testing and benchmarking of our new extended PRS model, we identified improved predictive accuracy of Lp(a) levels across diverse ancestries.

Conclusions: Collectively, our work proposes new ways to improve transferability of genetic testing for CVD across populations through structural analyses, and integration of polygenic burden and a locus of large effect. Building from this work will help narrow a current gap in genetic testing and ensure the promise of precision medicine is extended to all.

ABSTRACTS

Poster Number 23
Graduate Student
Heart Failure and Cardiomyopathy

MECHANISMS UNDERLYING DILATED CARDIOMYOPATHY ASSOCIATED WITH FKBP12 DEFICIENCY

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Background: Dilated cardiomyopathy (DCM), with estimated prevalence in the human population from 1 in 250 to 1 in 2500, is characterized by extensive cardiac remodeling leading to dilatation of the LV, fibrosis, LV posterior and septal wall thinning, and decreased contractility. Mutations in a wide variety of genes lead to DCM, but no common mechanism underlying the development of DCM has been identified.

Materials/Methods: To define the role the immunophilin FKBP12 in cardiac function, two conditional models of FKBP12 deficiency were created using *Fkbp1a* floxed (FL) mice expressing Cre⁺ recombinase under the control of different promoters (α -myosin heavy chain, α -MHC, and muscle creatine kinase, MCK) that differ in both developmental stage of expression (E9 versus E13) and Cre⁺ expression levels. Floxed mice and mice hemizygous for α -MHC-Cre⁺ recombinase only (controls for potential cytotoxic effects of the Cre⁺ recombinase) were used as controls. Echocardiography, Ca²⁺ imaging, and RNA-seq transcriptomic and pathway enrichment analysis with western blot validation were performed on 10 – 12-week-old mouse hearts.

Results: FKBP12 was reduced by 96% and 86% in α -MHC-Cre⁺ and MCK-Cre⁺ FKBP12-deficient adult mice, respectively, compared to FL mice. Of our four strains of mice, only the α -MHC-Cre⁺ FKBP12-deficient mice developed an early-onset dilated cardiomyopathy (DCM) and displayed increased cardiomyocyte sarcoplasmic reticulum Ca²⁺ leak. Gene expression changes in these hearts were associated with cardiotoxicity functions such as DCM and included large elevations in mRNA and protein levels of Ankyrin repeat domain 1 (*Ankrd1*), a negative regulator of cardiac gene expression.

Conclusions: These data suggest an FKBP12 deficiency that begins during cardiac development and reduces FKBP12 below a critical level causes RyR2 mediated Ca²⁺ leak and *Ankrd1* elevation, leading to cardiac structural remodeling and the development of DCM. This Ca²⁺ leak/*Ankrd1* pathway may represent a common and targetable mechanism for DCM.

ABSTRACTS

Poster Number 24
Graduate Student
Aortopathy and Valvular Heart Disease

A POPULATION-BASED STUDY OF AORTIC DISSECTION AMONG CHILDREN AND YOUNG ADULTS, 2004-2019

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Background: Aortic dissection (AD) in the young is extraordinarily rare, limiting the ability to ascertain population-based incidence. We aimed to calculate the population-based incidence of AD <40y, report associated diagnoses, and assess characteristics associated with inpatient mortality.

Materials/Methods: This retrospective cohort study evaluated unique hospitalizations for those <40y with AD from 2004-2019 in the Inpatient Public Use Data File, a population-based data source archiving virtually all Texas hospitalizations. Incidence was calculated by dividing AD hospitalizations by the annual Texas census counts by age group. Associated diagnoses based on International Classification of Disease (ICD9/10) codes were reported. For inpatient mortality analysis using mixed-effects log- binomial regression, covariates included age, sex, discharge year, and associated diagnoses.

Results: A total of 1,971 patients were hospitalized with AD (65.3% male), for a population-based incidence of 6.4/1 million person-years (95%CI 6.1-6.7). A bimodal distribution was observed, with 0.68 cases/1 million person-years for 0-4y followed by 0.34 cases/1 million person-years for 5-9y and 0.77 cases/1 million person-years for 10-14y. Among infants (<1y), 53.3% had diagnoses for trauma or CHD intervention while none had a diagnosed CTD. Conversely, among those ages 30-39y, trauma was comparatively less frequent (8.0%) while CTD was more frequent (7.5%). Overall mortality was 10.2%, with males at higher risk of death than females (RR 1.2, 95%CI 1.1-2.0, p=0.01). Compared to those without a CTD diagnosis, patients with a CTD diagnosis had lower mortality (RR 0.5, 95%CI 0.4-0.8, p=0.005). Mortality improved over time (13.7% in 1999-2004 vs. 7.5% in 2015-2019, p=0.001).

Conclusions: AD <40y is rare with a bimodal distribution and is associated with trauma in a large proportion of young children, while a larger proportion of young adults with AD have CTD. Mortality is lower in those with diagnosed CTD and has improved over time.

ABSTRACTS

Poster Number 25
Graduate Student
Heart Failure and Cardiomyopathy

AKAP12 INTERACTS WITH PHOSPHODIESTERASE 8A (PDE8A) AND B-ADRENERGIC RECEPTORS (ADRB2) IN CARDIOMYOCYTES

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Background: Heart failure (HF) is the leading cause of death in the United States and is a major cause of death globally. In HF, sympathetic stimulation of ADRB2 triggers cAMP-dependent Protein Kinase A (PKA) dependent phosphorylation of proteins that regulate cardiac function. cAMP levels are regulated in part by phosphodiesterases (PDEs). A Kinase Anchoring Proteins (AKAPs), a family of scaffolding proteins, play a crucial role in facilitating signal transduction by bringing together multiple signaling components. Previous studies have shown that AKAP12 couples to the ADRB2 and affects the agonist- induced association of AKAP12 and PDEs to the receptor. However, the interactive roles of AKAP12, ADRB2, and PDEs in cardiac function are unclear.

Materials/Methods: We investigated the interaction of AKAP12 with ADRB2 and PDE8A, a member of the PDE family, using primary ventricular cardiomyocytes (CMs) isolated from transgenic mice (8-12 weeks old). Contractile properties of the CMs were assessed using a Multi-Cell Lite® system (IonOptix), and protein colocalization of AKAP12 and PDE8A was evaluated by immunostaining using confocal microscopy.

Results: With the application of ADRB2 selective inhibitor ICI-118,551 and the non-selective ADRB agonist isoproterenol (ISO) together to isolated CMs and then measured the contractility and [Ca²⁺]_i. Results are comparably similar between AKAP12OX and AKAP12WT. However, when the PDE8A selective inhibitor PF-04957325 was applied during ISO stimulation, contractile results were significantly higher in AKAP12OX CMs. Moreover, confocal microscopy results showed increased AKAP12OX CMs colocalization with PDE8A with ISO stimulation.

Conclusions: We demonstrated for the first time that PDE8A is associated with AKAP12, and the signaling pathway is initiated from ADRB2.

ABSTRACTS

Poster Number 26
Graduate Student
Aortopathy and Valvular Heart Disease

WHOLE EXOME SEQUENCING UNCOVERS THE GENETIC COMPLEXITY OF BICUSPID AORTIC VALVE IN FAMILIES WITH EARLY ONSET COMPLICATIONS

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Background: Bicuspid aortic valve (BAV) is the most common congenital heart lesion with an estimated prevalence of 1%. While more than 50% of individuals with BAV undergo aortic valve surgery during their lifetimes, only 10% of patients with BAV require aortic valve surgery in the first two decades of life. We hypothesize that specific gene variants predispose to early onset complications of BAV (EBAV).

Materials/Methods: We analyzed whole exome sequences (WES) to identify rare coding variants that contribute to BAV disease in 215 EBAV families. Individuals included in this study met early onset criteria if they presented before age 30 with moderate or severe aortic stenosis or regurgitation (per American Society of Echocardiography guidelines), a large thoracic aortic aneurysm (Z-score > 4), aortic valve or aortic surgery, or aortic dissection.

Results: Predicted pathogenic variants of causal genes were present in 111 EBAV families (51% of total), including genes that cause BAV (9%) or heritable thoracic aortic disease (HTAD, 19%). After appropriate filtration, we also identified 139 variants in 55 novel genes that are associated with autosomal dominant congenital cardiac phenotypes, including recurrent deleterious variation of FBN2, MYH6, channelopathy genes, and type 1 and 5 collagen genes. We also found there was minimal genetic overlap between young individuals who present due to early onset valve complications and those who present due to early onset TAD.

Conclusions: These findings confirm our hypothesis that unique rare genetic variants drive early onset presentations of BAV disease. Our results suggest either that up to 50% of individuals with EBAV may exhibit mild or no features of a Mendelian disorder that includes cardiovascular anomalies, or that variants in such genes may cause isolated EBAV. Genetic testing for predictive variants in these candidate genes may eventually prove useful to identify patients who can benefit from more aggressive surveillance or therapies to prevent BAV complications.

ABSTRACTS

Poster Number 27
Graduate Student
Aortopathy and Valvular Heart Disease

A MULTICENTER RANDOMIZED CONTROLLED TRIAL OF EXERCISE IN AORTIC DISSECTION SURVIVORS

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Background: There are currently no evidence-based guidelines for exercise after thoracic aortic dissection (TAD), with highly variable recommendations that frequently lead patients to restrict their physical activities. This multicenter randomized controlled trial was intended to evaluate the safety and efficacy of a moderate-intensity guided exercise program for TAD survivors.

Materials/Methods: Participants were eligible for the trial if they had a Type A or Type B dissection at least 90 days before enrollment and could attend two in-person study visits to complete PROMIS surveys and 24-hour ambulatory blood pressure measurements (ABPM). Participants were randomly assigned to usual care or a guided exercise circuit of six moderate intensity exercises: bicep curls, wall sits, hand grips, leg raises, cycling, and treadmill. After a supervised session with exertional pressure measurements, they continued guided exercises at home with 3 virtual follow up visits.

Results: The first 38 participants completed supervised exercises without adverse outcomes, and only one participant developed severe hypertension (>210 mmHg). Mean PROMIS T scores for anxiety (51 ± 9), chronic pain (51 ± 7), and social impairment (54 ± 8) were increased at baseline. In ABPM data, nocturnal hypertension (83%) and blunted nocturnal dipping (40%) were relatively frequent. 13 participants (34%) developed exertional hypertension (>180 mmHg), and this was correlated with systolic hypertension and elevated blood pressure variability on ABPM. After 3 months, the mean number of exercise repetitions increased by 25% and grip strength increased by 30%.

Conclusions: Guided exercise is safe after TAD and improves key measures of cardiovascular fitness. The complete outcomes of the trial will be available in October 2024.

ABSTRACTS

Poster Number 28
Graduate Student
Arrhythmias and Channelopathies

LONG-TERM EFFICACY AND SAFETY OF CARDIAC GENOME EDITING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

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Background: Heterozygous autosomal-dominant single nucleotide variants in RYR2 account for 60% of cases of catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited arrhythmia disorder associated with high mortality rates. CRISPR/Cas9-mediated genome editing is a promising therapeutic approach that can permanently cure the disease by removing the mutant RYR2 allele. However, the safety and long-term efficacy of this strategy have not been established in a relevant disease model. The purpose of this study was to assess whether adeno-associated virus type-9 (AAV9)-mediated somatic genome editing could prevent ventricular arrhythmias by removal of the mutant allele in mice that are heterozygous for Ryr2 variant p.Arg176Gln (R176Q/+).

Materials/Methods: Guide RNA and SaCas9 were delivered using AAV9 vectors injected subcutaneously in 10-day-old mice. Injected mice were assessed using in vivo electrophysiology and echocardiography studies. Samples from injected mice were analyzed by histology, western blot, reverse transcriptase qPCR, and deep RNA sequencing.

Results: At 6 weeks after injection, R176Q/+ mice had a 100% reduction in ventricular arrhythmias compared to controls. When aged to 12 months, injected R176Q/+ mice maintained a 100% reduction in arrhythmia induction. Deep RNA sequencing revealed the formation of insertions/deletions at the target site with minimal off-target editing on the wild-type allele. Consequently, CRISPR/SaCas9 editing resulted in a 45% reduction of total Ryr2 mRNA and a 38% reduction in RyR2 protein. Genome editing was well tolerated based on serial echocardiography, revealing unaltered cardiac function and structure up to 12 months after AAV9 injection.

Conclusions: Taken together, AAV9-mediated CRISPR/Cas9 genome editing could efficiently disrupt the mutant Ryr2 allele, preventing lethal arrhythmias while preserving normal cardiac function in the R176Q/+ mouse model of CPVT.

ABSTRACTS

Poster Number 29
Graduate Student
CAD, Atherosclerosis, Ischemia

EFFECTS OF GLYCOCALYX MATURITY ON AORTIC ENDOTHELIAL CELL'S RESPONSE TO SHEAR STRESS

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Background: The endothelial glycocalyx (eGCX) is a crucial and understudied (in shear stress studies) component of endothelial cells in mammalian blood vessels, involved in mechanotransduction and vascular integrity. Dysregulation of the eGCX is linked to early onset cardiovascular diseases like atherosclerosis, characterized by plaque build-up and increased endothelial inflammation. This study hypothesizes that disturbed blood flow leads to eGCX degradation, resulting in endothelial dysfunction and endothelial-to-mesenchymal transition (EndMT) and the progression of atherosclerosis.

Materials/Methods: We aim to investigate the impact of fluid shear stress (uniform and disturbed) on eGCX integrity and its effect on EndMT in endothelial cells. Human Aortic Endothelial Cells (HAECs) will be cultured for 21 days and exposed to different shear stress levels (0, 5, and 35 dyne/cm²) to mimic static, disturbed, and laminar flow conditions, respectively. Wheat Germ Agglutinin (WGA) staining, an immunofluorescent technique that specifically binds to sialic acids on the terminal ends of the eGCX, will be used for eGCX visualization, complemented by DAPI staining for cell count normalization. A DMMB assay will quantify sulfated glycosaminoglycans (sGAGs). Biomarkers including CD36 for lipid uptake, MCP-1 and Nuclear Factor Kappa B for inflammation, ICAM-1, VCAM-1, and PECAM-1 for cell adhesion, and SNAIL-1, Vimentin, TGF-Beta, MMP2, P4HA1, and Alpha Smooth Muscle for End-MT will be analyzed to assess the cellular responses to shear stress.

Results: Data collection and analysis are underway, with preliminary findings to be reported upon completion.

Conclusions: The study's outcomes are expected to elucidate the mechanistic pathways linking shear stress, eGCX integrity, and endothelial cell function, thereby providing a deeper understanding of the molecular underpinnings of atherosclerotic progression.

ABSTRACTS

Poster Number 30
Graduate Student
Disease Modeling

CHARACTERIZATION OF SINGULAR AND COLLECTIVE CELL RESPONSE TO CHANGES IN DISTAL MECHANICAL ENVIRONMENT

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Background: It has been extensively published that cells exhibit different behaviors depending on the mechanical environments. Among the aspects that have been tested is the stiffness of the growth substrate. Multiple organs possess vastly different stiffness among its layers, which is dependent on aspects such as collagen composition, muscle fiber alignment, etc. Traction force microscopy (TFM) is a commonly used method to find the forces cell exert on their substrate. It has been studied that exerted forces, shape, and migration vary between normal and transformed cells. There is scant research into characterization of cell behavior and the effects of their mechanical environment beyond the immediate factors. This project aims to elucidate whether cells have the capacity to be affected by distal mechanical cues in a significant manner.

Materials/Methods: Characterization of the hydrogel stiffness is done by conventional uniaxial compression. Characterization of the surface roughness will be done via micro-indenter. For the characterization of cell behavior, we will use a modified TFM protocol, in which the conventional last step of taking a picture of the unstressed state of the hydrogel surface will be shifted towards the start of the process, before cell seeding. This is achieved by adding a non-deformable second layer of fluorescent beads at the bottom of the hydrogel, which allows for a series of scripts to correct the effects of human handling of gels.

Results: The most recent addition has been the realignment and matching scripts that prepare the images before PIV analysis. We used SURF points to increase robustness of the protocol and added functions to minimize the images sent for PIV, ensuring they truly are present on both images.

Conclusions: This being a process still in development, the following steps will be the optimization of hydrogel formulation protocols, optimization of the tracking bead layers, and the completion of the single and collective cell tracking scripts to the current workflow.

ABSTRACTS

Poster Number 31
Graduate Student
Disease Models

CO-CULTURE MODELS: 3D SCAFFOLDS AND THEIR DISEASE MODELING APPLICATIONS

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Background: 2D cell cultures have long been used in cellular research as a method to investigate interactions between cells and different environments. An additional area of research using 2D cell cultures is co-cultures, in which researchers investigate the interactions between different cell types and their intercellular communications. 3D cell cultures have been steadily increasing in use since their initial development due to factors such as the ability to more closely resemble a natural biological microenvironment and a supporting in-vitro ECM. Within the Grande-Allen Lab, 2D and 3D cell cultures have been used to investigate the pathophysiology of cardiovascular diseases such as discrete subaortic stenosis and investigate how cells from donors of genetic mutations (such as Turner's Syndrome) behave in biomimetic microenvironments under certain conditions. These 3D cell cultures have consisted of co-cultures between endocardial endothelial cells (EECs) and cardiac fibroblasts encapsulated in PEGDA hydrogels, tuned to replicate EEC environments with respect to stiffness and shear stress. Using this 3D co-culture research, we have extrapolated co-culturing information to apply to human intestinal organoids using biodegradable hydrogels to enhance the biomimetic characteristics of the microenvironment.

Materials/Methods: Using a PEG-PQ-PEG polymer, we have developed a biodegradable hydrogel that replicates gastrointestinal tract stiffness (3kPa - 10kPa) and allows for the co-culture of intestinal epithelial tissue and neuronal cells. ES-D3 differentiated neuronal cells are embedded within the hydrogel and innervate apically seeded intestinal epithelial cells, which are seeded on top of basement membrane proteins adhered to the hydrogel via a covalent charge from thiolated PDL.

Results: We hypothesize that this hydrogel will allow for the successful creation of a human intestinal organoid.

Conclusions: This model will be used to model disease mechanisms of human norovirus at an epithelial and neurological level.

ABSTRACTS

Poster Number 32
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

SEX-SPECIFIC RESPONSE TO GLUTATHIONE PRECURSORS IN THE OLD MOUSE HEART

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Background: Common features of the aging heart include dysregulated metabolism, inflammation, and fibrosis, which can all contribute to diastolic dysfunction. Imbalanced oxidative stress can exacerbate each of these conditions, worsening the age-related cardiac defects. Therefore, we hypothesized that increasing natural antioxidant defenses (glutathione) may favor a healthier cardiac aging phenotype.

Materials/Methods: Twenty-one-month-old mice were fed for 12 weeks with a diet supplemented in two glutathione precursors, Glycine and N-Acetyl Cysteine (GlyNAC) or with a control diet. Heart function was measured noninvasively and longitudinally at baseline and then every 6 weeks.

Results: We found that GlyNAC reduced the age-associated increase in left atrial volume in old male, but not in old female mice. It also improved exercise performance in males. Subsequent unbiased cardiac proteome analysis identified that GlyNAC modestly changed global protein expression in males and pointed to the significant changes in two pathways: mitochondria-metabolism and extracellular matrix. Further analysis performed on mitochondrial extracts determined that GlyNAC diet led to an increase in Ndufb8, a subunit of the mitochondrial respiratory chain complex. In the GlyNAC old male mitochondria, we found an improved catalytic activity for CPT1b and an increased CrAT activity. Both enzymes are involved in fatty acid metabolism. Hearts from GlyNAC-fed old males exhibited enrichment in Fmod, a protein that can inhibit collagen fibril formation, possibly reducing extracellular matrix stiffness. In females, the expression or enzymatic activities of these proteins were not affected by the GlyNAC-supplemented diet.

Conclusions: In summary, our study supports the concept that aged male and female hearts exhibit basic phenotypical differences that may affect the response to interventions. These observations may have direct relevance in cardiac gerontology.

ABSTRACTS

Poster Number 33
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

LNCRNA CIRCA PROTECTS AGAINST POST MYOCARDIAL INFARCTION REMODELING BY REGULATING HNRNPA1 FUNCTION IN THE HEART

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Background: Disruption of circadian rhythm is associated with cardiovascular diseases, but the exact molecular mechanism remains elusive. Via transcriptional profiling of murine hearts, we discovered a cardiac specific circadian lncRNA Circa, which is uniquely expressed in the cardiomyocytes (CM) of the adult mouse heart. Circa expression is increased postnatally and diminished after stress such as myocardial infarction (MI). Circa null mice exhibit exaggerated infarct and reduce cardiac function after MI. Ectopic expression of Circa protects CM from ischemia injury in vitro and reversed the exaggerated MI phenotype in Circa null mice.

Materials/Methods: To explore the molecular mechanism of Circa in CM, we utilized both mouse adult CM and human iPSC-CMs, by using In vitro CM ischemic condition and the tools including RNA immunoprecipitation (RIP), RNA Affinity Purification (RAP), Biotinylated RNA pull down assay, Mass spectrometry and Proximity ligation in situ hybridization (PLISH).

Results: We found that Circa is primarily localized in the nuclei where it associates with components or regulators of the spliceosome, including hnRNPA1(A1). Circa null mice showed hundreds of aberrantly spliced transcripts both at baseline and post MI in the heart. We found hnRNPA1 exit the nucleus during hypoxia, which is prevented by Circa. Cytosolic hnRNPA1 is associated with increased cell death in hypoxia.

Conclusions: In conclusion, our study suggest that LncRNA Circa may regulate alternative splicing by retaining hnRNPA1 in the nuclear and reducing its cytosol fraction to protect heart injury from ischemic injury.

ABSTRACTS

Poster Number 34
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

MODELING TANGO2-DEFICIENCY DISORDER WITH iPSC-CMS REVEALED POSSIBLE NAV1.5 DYSFUNCTION

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Background: Bi-allelic loss-of-function mutations in TANGO2 (Transport and Golgi Organization protein 2) cause a rare multiorgan genetic disorder. Despite normal cardiac function at baseline, metabolic stresses such as fasting can cause lethal cardiac arrhythmias. The molecular function of TANGO2 is poorly understood, and a cardiac model for studying cardiac crisis is lacking, which largely hinders the research for TANGO2-deficiency disorder (TDD).

Materials/Methods: We generated multiple TANGO2 deficient iPSC-CM lines from patient and healthy individual backgrounds, along with WT isogenic controls by adenoviral expression or CRISPR editing. Electrophysiological recordings using Real-Time Cell Analyzer, Ca²⁺ imaging, and SyncroPatch 384 were performed. A natural history study on a cohort of 78 patients was also performed.

Results: TANGO2 deficient iPSC-CM lines recapitulated key arrhythmic phenotypes typically seen in TDD patients, which is fully reversed by ectopic expressing WT TANGO2. The natural history study suggests that the intake of multivitamin/B-complex greatly diminished the risk of cardiac crises in TDD patients. In agreement with the clinical findings, we demonstrated that folate (B9) virtually abolishes arrhythmias in TDD iPSC-CMs. The folate's effect was blocked by the dihydrofolate reductase inhibitor methotrexate, supporting the need for intracellular folate to mediate antiarrhythmic effects. Mechanistically, we showed that at baseline condition, TDD iPSC-CMs have normal intracellular folate level, mitochondria OXPHOS and Ca²⁺ handling functions. The patch clamp study demonstrated prolonged action potential duration and reduced Na⁺ current in TDD iPSC-CMs, indicating possible dysfunction of Nav1.5 and other ion channels which may underline the pathogenesis of TDD-associated arrhythmias.

Conclusions: TDD may lead to dysfunction in Nav1.5 and other ion channels in cardiomyocytes and results in lethal arrhythmia. Folate may be a potential therapeutic agent to prevent cardiac arrhythmias for TDD patients.

ABSTRACTS

Poster Number 35
Postdoctoral Research Trainee
Arrhythmia and Channelopathies

LEFT-RIGHT DIFFERENCES IN WNT INHIBITION UNDERLIE A PRO-FIBROTIC MICROENVIRONMENT AND ATRIAL FIBRILLATION PREDISPOSITION FOR PITX2 DEFICIENCY

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Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, primarily occurring with advanced age, and is associated with an increased risk of stroke and heart failure. Common variation in the non-coding region of PITX2, the left-sided determining transcription factor, is the strongest genetic signature of AF risk.

Materials/Methods: As PITX2 risk alleles further enhance age-associated risk and are associated with decreased expression of PITX2 in the left atrium (LA), we utilized our well-characterized Pitx2 mouse model to study the effect of advanced age at single-cell resolution. We performed single nuclear RNA-sequencing (snRNA-seq) on the LA of 24-month-old heterozygous and littermate controls and compared with our previously reported 6-month-old datasets.

Results: We identified a gene signature of decreased Wnt-signaling inhibition from Pitx2-deficient cardiomyocytes and increased Wnt-associated activation of fibroblasts. Transgenic Wnt reporter mice demonstrate that Pitx2 deficiency increases LA Wnt-signaling to right atrial levels. Using a cre-dependent overexpression allele of Pitx2, PITX2 was able to drive Sfrp1 and Sfrp2, two secreted inhibitors of Wnt signaling, in right atrial cardiomyocytes. Histological analysis of aged Pitx2-deficient mice had increased LA fibroblast proliferation and interstitial fibrosis not previously seen in young animals. Furthermore, aged Pitx2-deficient mice were susceptible to atrial arrhythmogenesis when challenged by transesophageal pacing. Lastly, we demonstrate that pharmacological Wnt inhibition is sufficient to reduce fibroblast activation and proliferation in the Pitx2-deficient LA.

Conclusions: Collectively, these data indicate that reduced LA Pitx2 leads to increased left-sided Wnt signaling, resulting in LA remodeling and increased arrhythmia susceptibility with age. Furthermore, in functionally validating the Pitx2-Wnt-fibrosis signaling axis in the aging LA, our data provides new insights for both AF pathogenesis and therapeutic strategies.

ABSTRACTS

Poster Number 36
Postdoctoral Research Trainee
Cardiac Regeneration and Stem Cells

YAP INDUCES A NEONATAL LIKE PRO-RENEWAL NICHE IN THE ADULT HEART

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Background: After myocardial infarction (MI), adult mammalian hearts fail to regenerate, and the cardiac microenvironment is irreversibly disrupted. Inactivation of the Hippo signaling pathway in cardiomyocytes (CMs) induces heart renewal and rebuilds the post-MI microenvironment.

Materials/Methods: We used single-cell RNA-sequencing combined with spatial transcriptomics to examine cellular relationships within the microenvironment of two murine cardiac renewal models: adult hearts expressing a constitutively active YAP (YAP5SA), and neonatal hearts subject to MI.

Results: We found in both models a conserved, renewal competent CM cell state with high YAP activity (CM2). CM2 colocalized with cardiac fibroblasts (CFs) expressing complement pathway component 3 (C3), and macrophages (MPs) expressing complement C3a receptor (C3ar1) to form a pro-renewal cellular triad. C3 and C3ar1 loss-of-function suppressed CM proliferation in both neonatal injured hearts and adult YAP5SA hearts, and indicated that C3a signaling between CFs and MPs was required to assemble the CM2, C3+ CF, and C3ar1+ MP cellular triad.

Conclusions: Our results demonstrate that CM-YAP drives the coalescence of a pro-renewal niche, which requires complement pathway signaling, during in vivo cardiac renewal.

ABSTRACTS

Poster 37
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

A NOVEL GENE THERAPY CM-YAPON PROVIDES LONG-TERM PROTECTION AGAINST MYOCARDIAL INFARCTION

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Background: Myocardial infarction (MI) permanently damages cardiac function, affecting approximately 800,000 people in the United States annually. Our laboratory showed that activating YAP in cardiomyocytes (CMs) promoted cardiac regeneration and mitigated pathological remodeling in mouse and pig MI models. However, the risk of oncogenicity makes sustained YAP expression or activity untenable as a translational therapy.

Materials/Methods: To achieve fine-tuned temporal control of YAP activity, we developed a YAPon system regulating alternative splicing of active YAP, which translates full length YAP5SA only after exposure to a small molecule LMI070. Western blot (WB) and reporter assay were utilized to test YAPon system in vitro. Immunofluorescence (IF), Sirius red staining, echocardiogram (Echo), and Magnetic resonance imaging (MRI) were used to describe the phenotype in mouse heart.

Results: We generated AAV9-expressing YAPon (AAV9-cTnT-Xon-YAP5SA) and found that a single dose of LMI070 induced transient YAP5SA protein expression in CMs which degraded within one week. MI was induced two weeks after LMI070 or vehicle treatment. Surprisingly, hearts treated with LMI070 had improved cardiac function and reduced fibrosis compared to vehicle controls, as evidenced by EF, MRI, and Sirius red staining.

Conclusions: We develop a novel gene therapy CM-YAPon which provides prolonged protection against MI.

ABSTRACTS

Poster 38
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

GASDERMIN D PROMOTES ATRIAL ARRHYTHMOGENESIS VIA PYROPTOSIS-INDEPENDENT MECHANISMS

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Background: Atrial fibrillation (AF) is the most common arrhythmia and related to inflammation. Gasdermin D (GSDMD), especial for the N-terminal GSDMD is an important downstream effector to activate inflammasome and cell death. However, its mechanistic contribution to AF remains unclear. This study aims to elucidate the effect of atrial cardiomyocyte (ACM)-specific overexpression of NT-GSDMD on AF development and explore its molecular mechanism.

Materials/Methods: ACM-restricted NT-GSDMD overexpressed (aGDNT) mouse model was established by adeno-associated virus injection. Echocardiography and programmed intracardiac stimulation were used to measure atrial structure and AF susceptibility. Optical mapping, histology, flow cytometry and biochemistry were performed to explain the underlying arrhythmogenic substrates.

Results: We discovered that aGDNT mice developed increased AF inducibility, shortened action potential alternans, reduced conduction velocity and atrial fibrosis compared to control mice. For one thing, NT-GSDMD facilitated IL-1b secretion through plasma membrane pores from intact ACM, which elicited hyperinflamed macrophages infiltration. For the other thing, NT-GSDMD pore-forming on mitochondrial membranes caused its dysfunction and released mitochondrial ROS (mtROS), inducing spontaneous Ca²⁺ waves. Alanine mutations of NT-GSDMD residues suppressed both plasma membrane and mitochondrial pore formation, the associated release of IL-1b and mtROS, and reduced AF susceptibility. Moreover, treated with the mtROS inhibitor MitoTEMPO was sufficient to attenuate arrhythmic substrates and prevent AF development. Notably, genetical ablation of Gsdmd prevents spontaneous atrial fibrillation in a mouse model.

Conclusions: Our study demonstrate the ability of GSDMD pore as an executor of activating inflammatory response and inducing mitochondrial dysfunction to create various AF substrates. This work provides insight into a non-pyroptotic role for GSDMD pore in cardiomyocytes to drive atrial arrhythmogenesis.

ABSTRACTS

Poster 39
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

A NOVEL LMNA MUTANT (R225X) LEADS TO CARDIAC CONDUCTION DISORDERS

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Background: Cardiac conduction disorders (CCDs), including sick sinus syndrome, atrioventricular block (AVB), and bundle branch block, are common arrhythmic disorders. LMNA mutations affect the nuclear envelope proteins lamin A and lamin C, have been linked to CCDs in patients, yet the mechanistic connection remains largely unexplored.

Materials/Methods: The LMNA-R225X knock-in mice were generated using CRISPR/Cas9 technology. A comprehensive approach involving surface ECG, telemetry ECG, programmed electrical stimulation, and echocardiography was employed to characterize the cardiac phenotype. Masson's Trichrome staining, immunofluorescence staining, HE staining, Ca²⁺ imaging, and RNA sequencing were performed to elucidate the mechanistic underpinnings of CCDs.

Results: A heterozygous nonsense mutation (c.C673T, p.R225X) in LMNA was identified in a kindred and was associated with progressive CCDs and atrial arrhythmias. In the LMNA-R225X KI model, R225X-homozygous mice displayed bradycardia and first-degree AVB prior to death at the age of 2 weeks. R225X-heterozygous mice exhibited age-dependent progressive AVB ranging from first to third degree and increased susceptibility to the pacing-induced atrial fibrillation, prior to the development cardiomyopathy. Histological examinations showed increased fibrosis within the atrioventricular node (AVN) and nuclear morphological changes in AVN pacemaker cells of R225X-heterozygous mice. Ca²⁺ imaging study revealed the reduced spontaneous firing rate of the AVN pacemaker cells in R225X-heterozygous mice. Bulk RNA-seq sequencing of the dissected AVN tissue revealed a downregulation of mRNA levels for ion channels, including the SK3 channel in the R225X knock-in mice.

Conclusions: The LMNA-R225X mutation leads to progressive AVB prior to cardiomyopathy, primarily associated with increased fibrosis within the AVN and decreased SK3 channel expression in AVN pacemaker cells. This results in disrupted electrical conduction pathways and diminished pacemaker cell automaticity in the AVN.

ABSTRACTS

Poster 40

Postdoctoral Research Trainee

CAD, Atherosclerosis, Ischemia

LOSS OF PERICENTRIN GENE (PCNT) IN SMOOTH MUSCLE CELLS LEADS TO ATHEROSCLEROSIS

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Background: Microcephalic Osteodysplastic Primordial Dwarfism type II (MOPDII) is caused by biallelic loss-of-function variants in pericentrin (PCNT), and early onset coronary artery disease (CAD) is a complication of the syndrome. Histopathology of coronary arteries from MOPDII patients who died of CAD in their early 20's showed extensive atherosclerosis.

Materials/Methods: Hyperlipidemic mice with SMC-specific Pcnt gene deletion (PcntSMC^{-/-}) exhibited significantly greater atherosclerotic plaque burden compared to similarly treated littermate controls despite similar serum lipid levels.

Results: Loss of PCNT in SMCs activated heat shock factor 1 (HSF1) and consequently upregulated the expression activity of HMG-CoA reductase (HMGCR), the rate limiting enzyme in cholesterol biosynthesis. The augmented cholesterol biosynthesis in PcntSMC^{-/-} SMCs activated PERK signaling and increased SMC phenotypic modulation in PcntSMC^{-/-} SMCs compared to control SMCs. HSF1 and Perk inhibition individually blocked SMC phenotypic modulation in vitro. In addition mice when treated with the HMGCR inhibitor, pravastatin reduced plaque burden in hyperlipidemic PcntSMC^{-/-} mice compared to that of control mice.

Conclusions: These data support that loss of Pcnt gene in SMCs increases SMC phenotypic modulation and atherosclerotic plaque burden by activating HSF1/HMGCR/Perk pathway, and targeting this pathway with statins in MOPDII patients has the clinically potential to prevent premature CAD in these individuals.

ABSTRACTS

Poster 41

Postdoctoral Research Trainee
Arrhythmias and Channelopathies

SPEG MEDIATES INCREASED ATRIAL FIBRILLATION INCIDENCE IN CHRONIC KIDNEY DISEASE

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Background: CKD is a risk factor of cardiovascular morbidity and mortality due to the increased incidence of atrial fibrillation (AF). AF onset is known to be the consequence of cardiomyocyte intracellular calcium (Ca²⁺) mishandling where increased ryanodine receptor type 2 (RyR2) activity causes triggered activity. RyR2 activity is regulated by phosphorylation of serine 2367 (S2367) by the 'striated muscle preferentially expressed protein' (SPEG). Reduced RyR2 phosphorylation at S2367 increases the risk of AF. We hypothesized that changes in atrial SPEG underly the increased risk of AF in CKD.

Materials/Methods: CKD was mimicked in mice by the 5/6 nephrectomy model. AF inducibility was determined using intracardiac programmed electric stimulation. Echocardiography was used to analyze cardiac structure. RYR2 phosphorylation and SPEG levels were measured by western blotting. Intracellular Ca²⁺ dynamics were assessed by confocal microscopy.

Results: CKD mice showed increased serum phosphate (p<0.01), creatinine (p<0.001) and urea (p<0.001). AF incidence was 4-fold higher in CKD respect sham mice (p<0.05). CKD mice showed longer P waves (p<0.01) and greater left atrial growth than Sham (p<0.05). Ejection fraction was only reduced in CKD mice after 6 weeks of CKD progression (p<0.001). SPEG levels and RyR2 phosphorylation at S2367 were decreased in atria from CKD mice (p<0.05). Atrial cardiomyocytes from CKD mice exhibited altered Ca²⁺ handling, with decreased SERCA activity (p<0.05), increased spark- mediated diastolic Ca²⁺ leak (p<0.01) and increased NCX activity (p<0.05). Finally, CKD-induced AF onset was prevented in mice with a mutation that mimics RYR2 phosphorylation at SPEG site.

Conclusions: This study shows that SPEG levels are decreased in atria from CKD mice what induces increased RyR2 activity leading to increased AF incidence. By conserving RYR2 phosphorylation at Ser2367, CKD-induced AF was prevented. Thus, we propose SPEG as a possible therapeutic target to reduce the increased incidence of AF in CKD patients.

ABSTRACTS

Poster 42
Postdoctoral Research Trainee
Cardiac Regeneration and Stem Cells

YAP REJUVENATES CARDIOMYOCYTES BY REMODELING MITOCHONDRIAL SUBSTRATE UTILIZATION

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Background: Cardiomyocytes (CMs) are highly differentiated cells with poor renewal ability, an integral reason underlying heart failure. Cardiac regeneration is the central target for repairing an injured heart. However, the process of cardiomyocyte regeneration declines after birth, which is concomitant with the onset of cardiomyocyte maturation, with energy metabolism shifting from glycolysis to fatty acid usage. Our lab established that YAP activation induces CMs to undergo division, resulting in effective tissue renewal. But exactly whether and how Hippo-YAP signaling is involved in the CM metabolic remodeling to promote CM proliferation is still unclear.

Materials/Methods: By applying the Transmission Electron Microscopy (TEM) imaging and metabolomic study, we observed notable changes of mitochondrial morphology, as well as the mitochondria substrate utilization change in YAP induced CMs. With comprehensive bioinformatics analyses, combined with snRNA sequencing and a maternal high fat diet model, we established the Cpt1b inhibition with YAP activation. We further elucidated the Mef2a-Cpt1b cascade disruption upon YAP induction in CMs.

Results: Our research reveals that Hippo-YAP signaling facilitates CM cell cycle re-entry by reducing lipid utilization in CMs, thereby preserving mitochondrial homeostasis. YAP-induced mitochondrial substrate utilization change predominantly depends on reducing Cpt1b activity. Additionally, we identified Mef2a as a crucial activator for CM maturation, which was inhibited upon YAP overexpression, leading to decreased Cpt1b levels in CMs. Overloaded fat significantly enhanced fatty acid oxidation and maturation in neonatal CMs, partially counteracting YAP-mediated rejuvenation effects.

Conclusions: We elucidate a mechanistic framework by which YAP reverses metabolic maturation in cardiomyocytes, thereby facilitating heart regeneration. This insight advances our understanding of metabolic remodeling in heart regeneration and the therapeutic potential of YAP.

ABSTRACTS

Poster Number 43
Postdoctoral Research Trainee
Cardiac Regeneration and Stem Cells

GENOME-WIDE PROFILING OF TOP2B BINDING IN HUMAN CARDIOMYOCYTES TO UNDERSTAND DOXORUBICIN-INDUCED CARDIOTOXICITY

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Background: The Anthracycline Doxorubicin (Dox), which is prescribed in 32% of breast cancer patients, can cause irreversible left ventricular dysfunction and heart failure. Dox intercalates into DNA forming a ternary complex with TOP2B. This complex induces DNA double-strand breaks, mitochondrial dysfunction and apoptosis by activating the p53 transcription factor. TOP2B is essential for the cardiotoxicity observed in mice. In proliferating cells, TOP2B regulates DNA topology and interacts with CTCF and cohesin at topologically-associated domain boundaries. However, it is unknown whether these functions are maintained in terminally-differentiated cardiomyocytes.

Materials/Methods: To gain insight into the mechanisms behind Dox-induced cardiotoxicity, we have developed a human iPSC-derived cardiomyocyte (iPSC-CM) model to study the binding of these transcriptional regulators. We performed chromatin immunoprecipitation followed by sequencing (ChIP-seq) for TOP2B, CTCF, and RAD21 (a cohesin subunit) in iPSC-CMs.

Results: We find thousands of genomic regions that are bound by each of these factors. Half of the 5,289 TOP2B-bound regions are co-bound by CTCF and RAD21 suggesting roles for TOP2B in gene regulation and chromatin organization in cardiomyocytes as has been observed in other cell types. Indeed, TOP2B binding is enriched at promoter regions, and 85% of TOP2B binding locations overlap regions enriched for H3K27ac in heart ventricle tissue, compared to less than 1% of locations overlapping H3K27me3- or H3K9me3-enriched regions. TOP2B binding locations are enriched near genes associated with cardiac development and chromatin binding, and are enriched for transcription factor motifs including NFYC and NRF1. TOP2B-bound regions overlap seven SNPs associated with arrhythmia including the HCN4 locus, and four SNPs associated with heart failure including the ACTN2 locus.

Conclusions: Our data suggest that TOP2B associates with gene regulatory regions in cardiomyocytes that may be relevant to cardiovascular disease.

ABSTRACTS

Poster Number 44
Postdoctoral Research Trainee
Aortopathy and Valvular Heart Disease

CRITICAL ROLE OF ENDOTHELIAL INJURY IN THE INITIATION OF AORTIC DISSECTION

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Background: Ascending thoracic aortic dissection (ATAD) is a highly lethal condition. However, how the dissection forms and expands that allows blood to enter and travel along the aortic wall remains poorly understood. This study aimed to explore the molecular and cellular process that leads to the initiation and expansion of aortic dissection.

Materials/Methods: In a mouse model of sporadic aortic aneurysm and dissection (AAD) model induced by angiotensin II (Ang II) infusion, serial sectioning of the entire segment of dissected ascending aortas was performed. Molecular and cellular dynamics in the aortic wall were examined by single-cell transcriptome analysis. The impact of necroptosis (RIP3) and pyroptosis (GSDMD) of endothelial cells (EC) on ATAD formation was determined using EC-specific Rip3^{-/-} mice and EC-specific Gsdmd^{-/-} mice. EC gene expression was also examined in ascending aortic tissues of patients with ATAD.

Results: Histological staining revealed the primary tear and entry point of the dissection proximal to the dissected area. Multiple smaller tears, immune cell accumulation, and interlamellar elastic membrane disruption were detected in both proximal and distal regions, indicating stress on the entire intimal layer. scRNA-seq analysis indicated significant EC barrier dysfunction, and upregulation of pro-death genes (e.g., RIP3 and GSDMD) in ECs soon after Ang II infusion. These changes were associated with endothelial hyperpermeability. Significant EC death was also observed in human ATAD. Prevention of EC death with EC-Rip3^{-/-} and EC-Gsdmd^{-/-} led to preserved EC barrier function and aortic integrity, and a decrease in ATAD incidence. Blocking necroptosis/pyroptosis with necrosulfonamide reduced the ATAD.

Conclusions: Our study suggests endothelial dysfunction and subsequent damage occur early in AAD formation and contribute to the initiation of aortic dissection.

ABSTRACTS

Poster Number 45
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

HEART FAILURE AND ATRIAL FIBRILLATION DEVELOPMENT IN A NEW TRANSVERSE AORTIC CONSTRICTION MOUSE MODEL (MTAC)

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Background: Heart failure (HF) is the leading cause of death worldwide. Most large and small animal disease models of HF are based on surgical procedures. A common surgical technique to induce HF is transverse aortic constriction (TAC), which induces pressure overload, but conventional TAC (cTAC) procedure is a highly invasive surgery associated with severe inflammation and excessive perioperative deaths. Minimally invasive TAC (mTAC) emerged as a new HF model that does not require thoracotomy.

Materials/Methods: Both carotid's blood flow was analyzed by pulse doppler. Cardiac structure and function was analyzed by echocardiography. Cardiac fibrosis was assessed in paraffinized hearts by Masson's Trichrome stain. Intracellular Ca²⁺ handling was analyzed by confocal microscopy. Predisposition to ventricular and atrial arrhythmia was studied by pacing electrical stimulation.

Results: The mTAC model showed low procedure-related mortality. Right to left carotid ratio was higher in mTAC than Sham mice ($p < 0.001$). Ejection fraction was decreased in mTAC mice from the second week after surgery (32.4 ± 5.6 vs 60.6 ± 1.0 , $p < 0.001$) in all mice. Ventricles from mTAC mice were dilated compared to Sham ($p < 0.001$). Left atria was bigger in mTAC than Sham mice (6.6 ± 0.6 vs 3.1 ± 0.3 , $p < 0.01$). mTAC mice showed cardiac hypertrophy ($p < 0.01$) with increased ventricular fibrosis (7.9 ± 1.4 vs 1.3 ± 0.1 , $p < 0.05$) and cardiomyocyte hypertrophy (4001 ± 358.4 vs 3072 ± 164.5 , $p < 0.01$). Ventricular cardiomyocytes showed systolic dysfunction ($p < 0.01$) and increased diastolic Ca²⁺ leak ($p < 0.05$). Finally, mTAC mice showed increased atrial fibrillation inducibility from early stages ($p < 0.05$).

Conclusions: In conclusion, mTAC model recapitulates the characteristics found in HF patients and showed for the first time electrical and structural atrial remodeling that increases the predisposition to atrial fibrillation. Thus, mTAC is a good model for a mechanistic understanding of HF and HF-associated AF and the development of new therapeutic drugs treating these conditions.

ABSTRACTS

Poster Number 46
Postdoctoral Research Trainee
Cardiac Regeneration and Stem Cells

CD36-RETINOIC ACID-FABP5-PPAR δ SIGNALING AXIS MODULATES CARDIOMYOCYTES' ABILITY TO PROLIFERATE IN NEONATAL MICE

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Background: A pertinent question is why only a subset of fetal/neonatal cardiomyocytes (CMs) spontaneously proliferate. Using single-cell RNAseq, we previously showed a specific population of CMs that is more responsive to cell cycle induction. This population is characterized by expression of the transmembrane scavenger receptor, CD36 (fatty acid (FA) internalization receptor). Here, we aim to investigate the mechanism by which CD36 modulates CMs decision to enter into the cell cycle in neonatal P1 CMs.

Materials/Methods: We used single-cell RNAseq as well as transgenic and knock out mice models.

Results: CMs isolated from P1 CD36 knockout mice (CD36KO) showed 50% less proliferation capacity compared to WT P1 CMs. Interestingly, CD36KO mice are born with smaller hearts which contain fewer CMs. Furthermore, compared with WT littermates, which completely regenerate the heart apex following apical resection at P1, CD36KO showed minimal regenerative capacity. Bulk RNAseq data from the P1 CD36KO hearts showed significant downregulation in the expression of retinoic acid (RA)-dependent signaling genes (e.g., FABP5, PPAR δ and RXRa) and a significant increase in PPAR δ expression. Confirming a causal role of CD36 in CM proliferation, we found that Cd36 is crucial in regulating the entry and interactions of RA or retinoid precursors in CMs. The CD36+ FACS-sorted CMs express significantly higher levels of PPAR δ , RXRa, and FABP5 and lower levels of PPAR δ , which are crucial in regulating the response to cell proliferation. Furthermore, small molecule activation of PPAR δ doubled cell cycle entry in P1 CMs and completely restored proliferation in CD36KO CMs. These data suggest that CD36 is essential to prime CMs proliferation during development by regulating RA/FABP5/PPAR δ /RXR transcriptional signaling.

Conclusions: These findings suggest that the CD36-RA-FABP5-PPAR δ signaling axis modulates the CMs' ability of P1 to spontaneously enter the cell cycle.

ABSTRACTS

Poster Number 47
Postdoctoral Research Trainee
Aortopathy and Valvular Heart Disease

TFAM DRIVES COMPENSATORY INDUCTION OF NUCLEAR-ENCODED MITOCHONDRIAL GENES

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Background: Mitochondria are highly-responsive organelles with diverse functions. Mitochondrial transcription factor A (TFAM) serves as a pivotal regulator of mitochondrial biogenesis by inducing the replication and transcription of mitochondrial genome. Tfam disruption in mice causes cardiac dysfunction. In this study, we examined its role in maintaining mitochondrial integrity in aortic smooth muscle cells (SMCs) and protecting aortas from sporadic aortic aneurysm and dissection (AAD).

Materials/Methods: By applying single-cell RNA sequencing (scRNA-seq) and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) on ascending aortas of angiotensin II (Ang II)- or saline-infused mice, the transcriptomic and epigenomic dynamics of genes in mitochondrial functions in aortic SMCs were examined. The role of TFAM in SMC injury and AAD formation was determined in SMC-Tfam^{-/-} mice.

Results: ScRNA-seq analysis of aortas in Ang II-infused WT mice revealed a paradigm wherein AngII infusion caused downregulation of mitochondrial-encoded genes and an upsurge in the expression of nuclear-encoded mitochondrial related genes in SMCs. Remarkably, SMC-Tfam^{-/-} mice exhibited a substantial suppression of nuclear-encoded mitochondrial genes, with only negligible alterations in mitochondrial genes. ScATAC-seq illuminated that Ang II infusion caused an increase in chromatin accessibility of nuclear-encoded mitochondrial genes in SMCs in WT mice, that was however compromised in SMC-Tfam^{-/-} mice. Finally, SMC-Tfam^{-/-} mice manifested a pronounced susceptibility to AngII-induced SMC inflammatory response and death, aortic dissection and rupture in both thoracic and abdominal aortas.

Conclusions: Our study suggests that TFAM may play a pivotal role in epigenetic induction of nuclear- encoded mitochondrial genes. These findings not only improve our comprehension of TFAM's regulatory spectrum but also underscore the importance of the nuclear - mitochondrial interaction in maintaining mitochondrial homeostasis.

ABSTRACTS

Poster 48
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

A NOVEL TECHNIQUE FOR THE IMPLANTATION OF A WIRELESS TELEMETRY DEVICE IN A PORCINE MODEL AS A VALUABLE TOOL IN CARDIOVASCULAR RESEARCH

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Background: Telemetry devices play a crucial role in preclinical cardiovascular research, enabling continuous monitoring of physiological signals such as EKG, temperature, and respiration without disrupting animals. The EMKA manual recommends intra-abdominal placement, but this may cause discomfort to pigs due to their lying habits. Here, we introduce a new surgical technique for implanting wireless telemetry devices in a porcine model.

Materials/Methods: We present a new method for implanting a telemetry device to monitor physiological signals continuously. We used 40 Yorkshire pigs between 20-30 kg. Following thorough disinfection with alcohol, povidone-iodine, and isolation of the surgical area with a surgical drape, precise anatomical landmarks are identified to guide the incision, delineated by the spine, scapula, and trapezius muscle borders. A 2-inch longitudinal incision, laterally from the spine, is made with a 10 blade. Dissection is performed with electrocautery, ensuring complete fascial layer division of the trapezius muscle. Blunt dissection then creates a pocket in the inner fascial layer, accommodating the telemetry device. Before device insertion, the pocket is treated with a Vancomycin mixture for antimicrobial prophylaxis. Wires are trimmed and placed using a 14 Fr angiocath, ensuring proper orientation and minimal skin visibility. Leads are bundled and secured with heavy silks, ensuring optimal organization. Following device placement and verification of measurements, the site is closed by layers.

Results: All animals maintained a continuous signal postoperatively and reached their protocol endpoint. Of the 40 pigs, there were only 2 cases of infection. One resolved after switching to broader spectrum antibiotics; the second underwent surgical debridement and device explant.

Conclusions: We created a new surgical protocol that places the device on the back, allowing unrestrained movement without irritation and a strong, continuous signal with minimal risk of infection.

ABSTRACTS

Poster Number 49
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

YAP DEFINES METABOLIC MICROENVIRONMENT TO DRIVE CARDIAC FIBROSIS

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Background: In failing hearts, cellular metabolism and tissue microenvironment are significant altered despite that the underlying mechanisms remain unclear. Cardiac fibrosis, a common pathophysiology associated with various heart diseases, occurs from the excess deposition of extracellular matrix by cardiac fibroblasts (CFs). Inactivation of Hippo pathway in CFs lead to YAP activation that promotes fibrosis and inflammation. How CF YAP regulates metabolism and cell-cell communications are yet to be explored.

Materials/Methods: To study the role of Hippo pathway in CFs, we conditionally knocked out Lats1/2 specifically in the CFs of mouse hearts (Lats1/2CKO). We then performed metabolic approaches, single- nucleus RNA sequencing (snRNA-seq) and spatially resolved transcriptomic profiling (ST) of Lats1/2CKO and control hearts. To identify the cell-cell communications between Lats1/2CKO CFs and other cell types, we performed ligand-receptor analysis of the snRNA-seq data. The functions of Lats1/2CKO CFs sending and receiving signals were tested by pharmacologic inhibitors.

Results: Metabolic approaches, snRNA-seq and ST analyses revealed that Hippo-deficient CFs activated glycolysis and increased cell plasticity during fibrosis and inflammation. Glycolysis inhibition abolished Hippo-deficient CF proliferation and fibrosis. To investigate the role of macrophages (Mac) in this context, we blocked Mac expansion pharmacologically and found that Hippo-deficient CF proliferation, cell plasticity and fibrosis were significantly reduced, suggesting that Macs promoted Hippo- deficient CF proliferation, plasticity and fibrosis. Sequencing analyses and functional studies showed that Macs secreted insulin-like growth factor 1 (IGF1) to activate IGF1 signaling in Hippo-deficient CFs to induce cell proliferation and fibrosis.

Conclusions: CF YAP upregulates glycolysis and promotes CF-Mac communications to induce CF plasticity, fibrosis and inflammation.

ABSTRACTS

Poster Number 50
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

NOVEL REV-ERB SPECIFIC AGONIST IMPROVES LEFT VENTRICULAR DYSFUNCTION AFTER PRESSURE OVERLOAD VIA TRANSCRIPTION REPRESSION

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Background: Circadian clock plays a vital role in heart health and diseases. The nuclear receptors Rev-erb α/β are key components of the circadian clock and play critical roles in cardiac remodeling after pressure overload. However, widely used REV-ERB agonist SR9009 has recently been reported to have off-target effects in several model systems. This study aims to test the effect of a structurally distinct, novel REV-ERB α/β agonist (P-1799) on left ventricular (LV) dysfunction and remodeling after pressure overload and investigate the molecular function of REV-ERB in cardiac remodeling.

Materials/Methods: Wild-type (WT) C57BL/6J or cardiac-specific Rev-erb α/β total knockout (cTKO/TKN1N2) mice underwent Sham or transverse aortic constriction (TAC) surgeries at the age of 9 weeks. After TAC, mice were injected with P-1799 at a dose of 20 mg/kg/day or Vehicle via intraperitoneal injection once daily at zeitgeber time ZT2. Then the apex of the WT mice heart were applied for snRNA-Seq analysis (10X Genomics, CA).

Results: 6 weeks after TAC, WT mice in the 1799-TAC group showed a significantly improved LV ejection fraction (EF) and lower LV mass compared to WT mice in the Vehicle-TAC group. Both the cross-section sizes of the cardiomyocytes and the fibrosis area were smaller in WT mice of the 1799-TAC group compared to the vehicle group. However, in cTKO mice P-1799 did not show any effect. The results of snRNA-seq showed that P-1799 reversed the altered transcriptomic profile induced by TAC in CM and FB via transcription repression.

Conclusions: The novel REV-ERB agonist P-1799 demonstrated cardiac protection post-pressure overload in both prevention and treatment models. Mechanistically, P-1799 activates REV-ERBs preventing the aberrant gene program induced by TAC, thereby maintaining normal myocardial metabolism and cardiomyocyte subpopulations. These findings underscore REV-ERBs' role in cardiac remodeling, positioning P-1799 as a potential proto-drug for heart failure therapy.

ABSTRACTS

Poster Number 51
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

DNA DOUBLE-STRANDED BREAKS, A HALLMARK OF AGING, DEFINED AT THE NUCLEOTIDE RESOLUTION, ARE INCREASED AND ASSOCIATED WITH TRANSCRIPTION IN THE CARDIAC MYOCYTE GENOME IN LMNA-CARDIOMYOPATHY

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Background: An intrinsic feature of gene transcription is the formation of DNA superhelices near the transcription bubble, which are resolved upon induction of transient double-stranded breaks (DSBs) by topoisomerases. Unrepaired DSBs are pathogenic as they lead to cell cycle arrest, senescence, inflammation, and organ dysfunction. We posit that DSBs would be more prevalent at the genomic sites associated with gene expression. The objectives were to identify and characterize genome-wide DSBs at the nucleotide resolution and determine the association of DSBs with transcription in cardiac myocytes.

Materials/Methods: We identified the genome-wide DSBs in ~ 1 million cardiac myocytes per heart in 3 wild-type and 3 myocyte-specific LMNA-deficient (Myh6-Cre:LmnaF/F) mice by END-Sequencing, the Lamin associated domains (LADs) were defined in cardiac myocytes via CUT&RUN assay (N=5).

Results: The prevalence of DSBs was 0.8% and 2.2% in the wild-type and Myh6-Cre:LmnaF/F myocytes, respectively. The END-Seq signals for 8 DSBs were enriched in the wild-type and 6,764 in Myh6-Cre:LmnaF/F myocytes, respectively ($p < 0.05$). The DSBs were preferentially localized to the gene regions, transcription initiation sites, cardiac transcription factor motifs, and G quadruplex forming structures. We found an average of 818 LADs per myocyte, LADs that were shared by at least three mice ($N = 2,572$) were considered constitutive LADs (cLADs), which comprised about a third of the myocyte genomes. Transcript levels of the protein-coding genes located at cLADs ($N = 3,975$) were ~ 16- fold lower than those at non-LAD regions ($N \sim 17,778$). The prevalence of DSBs was higher in the non- LAD as compared to the cLAD regions.

Conclusions: To our knowledge, this is the first identification of DSBs, at the nucleotide resolution in the cardiovascular system. The prevalence of DSBs was higher in the genomic regions associated with transcription. Because transcription is pervasive, DSBs are expected to be common and pathogenic in various disease states and aging.

ABSTRACTS

Poster Number 52
Postdoctoral Research Trainee
Aortopathy and Valvular Heart Disease

THE EXPRESSION PROFILE OF PROTEOGLYCANS IN ASCENDING THORACIC AORTIC ANEURYSM AND DISSECTION: INSIGHTS FROM SINGLE CELL TRANSCRIPTOME ANALYSIS OF HUMAN AND MOUSE AORTAS

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Background: Proteoglycans (PGs) play critical roles in maintaining normal aortic wall structure and function. However, abnormal accumulation of PGs, particularly large extracellular PGs, is often observed in thoracic aortic aneurysms and dissections (TAAD) and is suggested to promote aortic destruction. As the underlying mechanisms of PG accumulation in TAAD are poorly understood, we examined the dynamic expression of large extracellular PGs in ascending TAAD.

Materials/Methods: Single cell RNA sequencing (scRNA-seq) was performed in ascending aortic tissues from patients with aortic aneurysm (ATAA) or dissection (ATAD) and from normal transplant donor controls. scRNA-seq analysis was also performed in ascending aortas from angiotensin II (Ang II) infused mice, an established TAAD model. The role of STING—a potential driver of aortic degeneration—in PG expression was determined by comparing wild-type (WT) and Sting knockout mice.

Results: We observed that versican was abundantly expressed, while aggrecan exhibited relatively lower expression; brevican and neurocan were barely detectable. Versican and aggrecan were mostly expressed in fibroblasts (FBs) and smooth muscle cells (SMCs), and their expression progressively increased from control to ATAA to ATAD in both SMCs and FBs, particularly in pro-inflammatory FBs. Versican was undetectable in macrophages in control tissues, but was expressed in macrophages in diseased tissues. The upregulation of versican and aggrecan in SMCs, FBs, and macrophages was also observed in Ang II-infused WT mice; this induction was partially prevented in Sting knockout mice, suggesting the importance of STING in PG induction in AAD.

Conclusions: Versican and aggrecan are mostly expressed in aortic FBs and SMCs, and their expression is progressively increased from control to ATAA to ATAD. STING may be involved in PG induction. The increased expression of versican and aggrecan may contribute to abnormal accumulation of large PGs in TAAD.

ABSTRACTS

Poster Number 53
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

NUMB FAMILY PROTEINS REGULATE LEFT VENTRICULAR COMPACTION BY MODULATING AUTOPHAGIC PROCESS

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Background: Left ventricular noncompaction (LVNC) is a type of cardiomyopathy. The pathogenesis of LVNC is unclear, and whether LVNC is an acquired or congenital cardiomyopathy is controversial. We previously found that the ablation of Numb, an endocytic adaptor protein, and its homologue Numbl at early stage, causes defects in trabeculation and compaction resulting in embryonic lethality. In this study, we found that Numb and Numbl deletion specific in the heart at later stage causes LVNC cardiomyopathy.

Materials/Methods: We applied aMHC-Cre to delete Numb and Numbl to generate double knockout (ADKO); determine the pathophysiology via echocardiography (ECHO) and histology; determine the heart arrhythmia via Telemetry; examine the heart structure and functions via ECHO; examine Numb subcellular localization via Numb overexpression line (R26-Flag:mCherry:Numb); determine proteins that interact with Numb via mass spectrometry; determine the mechanistic function of NFPs in autophagy via autophagy reporter, electron microscopy, and molecular and biochemical assays.

Results: The ADKO died between eight- and twelve-month-old. The ADKO hearts display LVNC by two months old, a reduced diastolic function by one month old, a reduced systolic function by four months old. ADKO hearts also manifest clinical signs of LVNC, including arrhythmias, thrombosis, and sudden death. ADKO hearts exhibit significant accumulation of damaged mitochondria, autophagosomes and autophagolysosomes. And ADKO hearts exhibit abnormal autophagic flux. Mass spectrometry analyses reveal Numb's interaction with proteins involved in endocytosis and autophagy. Consistently, numb localizes to autophagosomes and autophagolysosomes.

Conclusions: NFPs deletion in cardiomyocytes interferes the endocytosis and autophagic flux, which results in the abnormal compartment of multiple proteins in the myocardium. Our study suggests that NFPs mediated endocytosis and autophagy are essential for left ventricular compaction.

ABSTRACTS

Poster Number 54
Postdoctoral Research Trainee
Heart Failure and Cardiomyopathy

GENETIC DELETION OF HISTONE LYSINE DEMETHYLASE KDM5A IN CARDIOMYOCYTES ATTENUATES LMNA-ASSOCIATED DILATED CARDIOMYOPATHY

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Background: Heart failure (HF) is a major cause of morbidity and mortality. Hereditary cardiomyopathies are the prototypic forms of HF. Notable among them is dilated cardiomyopathy (DCM) caused by mutations in the LMNA gene, encoding Lamin A protein (LMNA-DCM). We have recently shown that KDM5A, a histone H3 lysine 4 demethylase, is activated in the hearts of human patients and mouse models of LMNA-DCM and KDM5 inhibition in iPSC derived cardiomyocytes induced expression of genes involved in oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO). Thus, we hypothesized that activation of the KDM5A in the LMNA-DCM is pathogenic and contributes to cardiac dysfunction.

Materials/Methods: The *Lmna* and *Kdm5a* genes were concomitantly deleted in the cardiac myocytes (CMs) in mice using cre recombinase and the effects of KDM5a deletion on cardiac function and survival was evaluated.

Results: CM-specific deletion of the *Lmna* gene (Myh6-Cre:*Lmna*F/F), representing a mouse model of LMNA-DCM, led to severe cardiac dysfunction, increased apoptosis, and premature death, as published. The Myh6-Cre:*Kdm5a*F/F mice showed no discernible phenotype. Deletion of the *Kdm5a* gene in CMs in the LMNA-DCM mice (Myh6-Cre:*Lmna*F/F:*Kdm5a*F/F) attenuated myocardial apoptosis, improved cardiac function, and prolonged survival. The median and maximum survival times were increased by ~ 40 to 50% in the Myh6-Cre:*Lmna*F/F:*Kdm5a*F/F. Analysis of the CM transcripts by RNA-sequencing showed differential expression of 6609 genes in the Myh6-Cre: *Lmna*F/F CMs and 2791 genes were attenuated in the Myh6-Cre:*Lmna*F/F:*Kdm5a*F/F. Pathway analysis showed that genes involved in FAO and OXPHOS were the most suppressed in LMNA-DCM and were rescued upon *Kdm5a* deletion.

Conclusions: Deletion of the *Kdm5a* gene in the LMNA-DCM mice imparts salubrious effects by prolonging survival and improving cardiac dysfunction, and upregulating genes involved in OXPHOS and FAO.

ABSTRACTS

Poster Number 55
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

TANGO2 DEFICIENCY AFFECTS LIPID METABOLISM IN CARDIAC MYOCYTES

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Background: Tango2 deficiency disorder (TDD) is a multisystem disease marked by recurrent episodes of sudden hypotonia, loss of motor control and metabolic crisis. During metabolic crisis, TDD patients can develop fatal cardiac arrhythmias. However, the role of TANGO2 in mammalian cells is unknown.

Materials/Methods: We have cultured WT and TANGO2 knockout (KO) iPSC-derived cardiomyocytes (iPSC-CM) and HEK293 in media supplemented with 400uM oleic acid to promote the accumulation of neutral lipids in lipid droplets. The cells were then subjected to starvation conditions, HBSS for iPSC-CM or DMEM containing no glucose and no serum for HEK293. Starvation was done in the presence or absence of Bafilomycin, an inhibitor of autophagy.

Results: We have shown altered lipid droplet metabolism in cells lacking TANGO2. TANGO2 KO iPSC-CM have increased number and size of lipid droplets (LD) relative to WT, and this difference increases following starvation. Transfection of TANGO2 KO HEK293 cells with WT TANGO2 decreases the average size of LD. Decreased amounts of LAMP1 and elevated levels of LC3II in TANGO2 KO HEK293 cells may indicate a dysfunction in the endolysosomal compartments. While blocking autophagy increases the number of LD per cell in WT HEK293 it does not change the number of LD per cell in TANGO2 KO HEK293 cells.

Conclusions: Together these findings suggest a role for TANGO2 in the metabolism of LD through lipophagy. We are continuing to investigate whether abnormal metabolism of LD in cardiomyocytes contribute to the cardiopathology of TDD.

ABSTRACTS

Poster Number 56
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

CRISPR-BASED GENOMIC DELETIONS OF CANDIDATE ENHANCER ELEMENTS ASSOCIATED WITH QT INTERVAL VARIATION

Ambreen Asim¹, Ashish Kapoor¹, Kyla Vickery¹
¹Center for Human Genetics, UT Health Science Center

Background: Electrocardiographic QT interval (QT_i), an index of ventricular de- and re-polarization, is a clinically significant, heritable quantitative trait. Prolongation or shortening of QT_i is associated with increased risk for cardiac arrhythmias and sudden cardiac death. Genome-wide association studies (GWAS) of QT_i have identified trait-associated common noncoding variants at dozens of loci, including at SCN5A and NOS1AP. Following a cis-regulatory mechanistic hypothesis underlying GWAS loci, we performed luciferase assay-based enhancer screens, and identified five and six enhancer variants at the SCN5A and NOS1AP loci, respectively.

Materials/Methods: Our aim here is to design effective paired guide RNAs (gRNAs) for CRISPR-based genomic deletions of these enhancer elements by introducing two double-strand breaks and deletion of the intervening sequence by nonhomologous end joining-mediated repair. To test the efficacy of our designed gRNAs, we evaluated them for introducing genomic deletions in 293T and AC16 cells.

Results: We designed a pair of gRNAs, within 500 bases upstream and downstream of the genomic target, using five gRNA-designing tools, and selected the ones highly recommended by at least three gRNA-designing tools. We used Bowtie2 alignment to ensure that the gRNAs have a single hit in the human genome. Protospacers were cloned in pX330 vector designed for dual expression of gRNAs and Cas9. 293T/AC16 cells transfected with gRNAs/Cas9 constructs were harvested 48h post transfection, and isolated genomic DNA was evaluated by PCR using a set of primers upstream and downstream of gRNA cleavage sites. Deletion bands were detected for all 11 targeted elements in both cell lines, indicating the efficacy of our designed gRNAs.

Conclusions: We assessed the efficacy of designed gRNAs to induce the desired deletions in two cell lines. In future, we will use these validated gRNAs to delete the candidate enhancer elements in human iPSC-CMs to assess endogenous activities and impacts on target gene expression.

ABSTRACTS

Poster Number 57
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

CRISPR-BASED GENOMIC DELETIONS OF CANDIDATE ENHANCER ELEMENTS ASSOCIATED WITH QT INTERVAL VARIATION

Ambreen Asim¹, Kyla Vickery¹, Ashish Kapoor¹
¹Center for Human Genetics, UT Health Science Center

Background: Electrocardiographic QT interval (QT_i), an index of ventricular de- and re-polarization, is a clinically significant, heritable quantitative trait. Prolongation or shortening of QT_i is associated with increased risk for cardiac arrhythmias and sudden cardiac death. Genome-wide association studies (GWAS) of QT_i have identified trait-associated common noncoding variants at dozens of loci, including at SCN5A and NOS1AP. Following a cis-regulatory mechanistic hypothesis underlying GWAS loci, we performed luciferase assay-based enhancer screens, and identified five and six enhancer variants at the SCN5A and NOS1AP loci, respectively.

Materials/Methods: Our aim here is to design effective paired guide RNAs (gRNAs) for CRISPR-based genomic deletions of these enhancer elements by introducing two double-strand breaks and deletion of the intervening sequence by nonhomologous end joining-mediated repair. To test the efficacy of our designed gRNAs, we evaluated them for introducing genomic deletions in 293T and AC16 cells.

Results: We designed a pair of gRNAs, within 500 bases upstream and downstream of the genomic target, using five gRNA-designing tools, and selected the ones highly recommended by at least three gRNA-designing tools. We used Bowtie2 alignment to ensure that the gRNAs have a single hit in the human genome. Protospacers were cloned in pX330 vector designed for dual expression of gRNAs and Cas9. 293T/AC16 cells transfected with gRNAs/Cas9 constructs were harvested 48h post transfection, and isolated genomic DNA was evaluated by PCR using a set of primers upstream and downstream of gRNA cleavage sites. Deletion bands were detected for all 11 targeted elements in both cell lines, indicating the efficacy of our designed gRNAs.

Conclusions: We assessed the efficacy of designed gRNAs to induce the desired deletions in two cell lines. In future, we will use these validated gRNAs to delete the candidate enhancer elements in human iPSC-CMs to assess endogenous activities and impacts on target gene expression.

ABSTRACTS

Poster Number 58
Postdoctoral Research Trainee
Arrhythmias and Channelopathies

MASSIVELY PARALLEL REPORTER ASSAYS TO IDENTIFY ENHANCER VARIANTS UNDERLYING QT INTERVAL GWAS LOCI

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Background: Electrocardiographic QT interval (QTi), a measure of ventricular de- and re-polarization, is a clinically relevant, moderately heritable trait associated with risk of cardiac arrhythmias. GWAS of QTi have identified dozens of noncoding variants-based loci, but the underlying mechanisms remain largely unknown. Based on a cis-regulatory mechanistic hypothesis for GWAS signals in the noncoding genome, we aim to use massively parallel reporter assays (MPRA), to screen and identify enhancer variants at 12 QTi GWAS loci.

Materials/Methods: We used a recently published QTi meta-analysis GWAS to identify associated variants. 300-base long oligos were designed and synthesized, with the target variant in three distinct 229-base long flanking sequence contexts. MPRA was performed in mouse cardiomyocyte HL1 cells.

Results: We identified 15,455 associated variants across the 12 QTi GWAS loci, of which 1,189 variants overlapping cardiac open chromatin regions were filtered for MPRA. 142,680 unique oligos, across two equally sized pools, representing both alleles of all variants in three different flanking sequence contexts, each linked to 20 distinct barcodes were synthesized. The oligo pools were cloned into pGL4.23 and propagated in DH10 β cells with >100 $\times$ coverage (>7.2 million clones per pool) to preserve library complexity. 48h post transfection, barcode sequencing libraries from HL1 cDNA (six replicates) and input plasmid (3 replicates) were generated, and are undergoing sequencing. Reporter activity at the barcode level in each replicate will be quantified by calculating the log2-transformed ratio of sequence depth- normalized cDNA/input plasmid read counts, and averaged across replicates and corresponding barcodes to determine test element-level activity.

Conclusions: We successfully designed and propagated MPRA libraries to evaluate 1,189 variants en masse. We expect our MPRA-based screen to identify several enhancer variants underlying QTi GWAS loci.

ABSTRACTS

Poster Number 59
Postdoctoral Research Trainee
Cardiorespiratory

AUTOMATED RESPIRATORY AND CARDIOVASCULAR DATA PIPELINE FOR WAVEFORM CHARACTERISTIC ANALYSIS

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Background: To better understand the mechanisms underlying respiratory and cardiovascular diseases, precise measurement and analysis of cardiorespiratory outcomes in rodent models are critical. While whole-body barometric plethysmography is a standard for studying respiratory functions in rodents, our Breathe Easy extension adds a pivotal dimension by analyzing heart rate (HR) alongside breathing outcomes. Our novel open-source Breathe Easy pipeline processes raw recordings and metadata into refined outcomes, creating publication-grade graphs and robust statistical analyses. This user-friendly platform includes the Signal Analysis Selection and Segmentation Integration (SASSI) program for selecting high-quality breaths and the STatistics and Graph Generator (STAGG) for advanced modeling.

Materials/Methods: Significantly enhancing its utility, the Breathe Easy extension seamlessly incorporates ECG data analysis, featuring a proprietary algorithm that precisely detects HR and R-R intervals. By integrating respiratory traces with cardiovascular metrics, this tool enables the comprehensive examination of the intricate interplay between these systems.

Results: Validation against expert manual selection confirmed the superior quality of Breathe Easy's data processing. We show two examples of biological application with animal models of Alzheimer's and Sudden Unexpected Infant Death (SUID), showcasing its analytical capabilities.

Conclusions: Breathe Easy stands out as a customizable and efficient solution for large-scale data handling and analysis, paving the way for machine learning applications in high-throughput studies. To understand respiratory and cardiovascular disease mechanisms, we must first optimize measurement and analyses of cardiorespiratory outcomes in rodent models.

ABSTRACTS

Poster 60
Postdoctoral Research Trainee
Cardiorespiratory

POTENTIAL CARDIOVASCULAR MECHANISMS OF AUTORESUSCITATION FAILURE IN SUDDEN INFANT DEATH SYNDROME BY ABERRANT NA OR 5-HT FUNCTION

Savannah Lusk¹, Christopher S Ward², Javier Hernandez¹, Russell S Ray¹

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Background: Sudden Infant Death Syndrome (SIDS) remains a top cause of infant death globally, and impaired autoresuscitation may be pivotal in SIDS cases. Abnormalities in the brain's serotonergic (5-HT) and noradrenergic (NA) systems, crucial for breathing, have been found postmortem in SIDS infants.

Materials/Methods: Our study engineered unique mouse models to dissect the roles of these systems in neonatal autoresuscitation. Using Cre- and FLPo-recombinase lines along with DREADD lines, we could independently or jointly stimulate or suppress the 5-HT and NA systems in neonates. Eight mouse models were created to represent different 5-HT and NA interventions. The autoresuscitation reflex was tested on our robotic assessment platform, Looper, until failure, with data analyzed by our Breathe Easy software.

Results: Out of 320 mice, those with NA or 5-HT activation alone, or in combination with NA activation, had lower auto-resuscitation success. These groups showed an increased heart rate at baseline, which persisted and rose through recovery phases, unlike other groups. Ventilatory parameters increased only when NA was activated. Together, the data suggest a cardiovascular, not respiratory, failure mechanism in the autoresuscitation reflex.

Conclusions: Our innovative approach, manipulating both 5-HT and NA systems, offers insights into their interaction with SIDS, indicating a complex interplay that could inform future research into its multifaceted causes.

ABSTRACTS

Poster Number 61
Postdoctoral Research Trainee
Cerebrovascular Response to Trauma

ALTERED BLOOD-BRAIN BARRIER AND PLATELET DYNAMICS IN THE UNINJURED CONTRALATERAL CORTEX FOLLOWING TRAUMATIC BRAIN INJURY IN MICE

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Background: Platelets are the smallest cells in the blood and are important in a variety of human conditions independent of their role in clotting. One of these conditions is traumatic brain injury (TBI), a disorder affecting a large number of individuals which can result in symptoms that persist throughout the lifetime of an individual, severely affecting quality of life. The role of platelets in the cortical response to TBI is not well understood. We hypothesize that TBI results in pathological platelet-microvessel interaction and platelet extravasation in the contralateral cortex following injury.

Materials/Methods: C57BL/6 mice were placed in a stereotaxic device and a head stabilizing plate was secured to the skull, a craniectomy performed (contralateral to the injury site) and a stacked-glass cranial window installed. The window and headplate were secured with dental resin, the surgical site closed, and the animal allowed to recover for three weeks prior to controlled cortical impact injury (2 mm impact tip, 3 m/s, 1 mm depth). Animals were imaged using an Andor CSU-W1 spinning disc confocal microscope.

Results: Cortical vasculature underlying the contralateral cranial window showed no gross alterations up to 6-months following cranial window installation. The combined model of controlled cortical impact injury following installation of a cranial window produced reliable and reproducible injury that can be tuned for injury severity. Here we show, for the first time, evidence of extensive platelet adhesion, platelet extravasation and blood-brain barrier disruption in the uninjured cortical vasculature and parenchyma of the contralateral cortex following severe TBI.

Conclusions: Here we show that TBI results in cerebrovascular changes in the contralateral cortex, far from the site of injury, and that altered platelet dynamics occur in the cortical vasculature. Furthermore, platelet extravasation into the brain parenchyma may play a role in the altered blood-brain barrier dynamics that follow this debilitating injury.

ABSTRACTS

Poster Number 62
Clinical Fellow/Resident
Arrhythmias and Channelopathies

CLONAL HEMATOPOIESIS IN TET2 AND ASXL1 IS ASSOCIATED WITH ATRIAL FIBRILLATION

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¹Internal Medicine, Baylor College of Medicine, Houston, TX; ²Medicine/Cardiology, Baylor College of Medicine; ³Cardiovascular, Mayo Clinic; ⁴Cardiovascular, Massachusetts General Hospital; ⁵Medical Oncology, Dana-Farber Cancer Institute; ⁶Epidemiology, Johns Hopkins Bloomberg School of Public Health; ⁷Epidemiology, University of Texas; ⁸Medicine, University of Minnesota; ⁹Medicine, Vanderbilt University; ¹⁰Medicine, Harvard Medical School; ¹¹Medicine, University of Texas Southwestern

Background: Clonal hematopoiesis of indeterminate potential (CHIP) may contribute to atrial fibrillation (AF) risk through its association with inflammation and cardiac remodeling. We studied the association of CHIP with AF, inflammatory and cardiac biomarkers and cardiac structural changes.

Materials/Methods: This prospective cohort study included 199,982 adults with exome sequencing (ES) from the Atherosclerosis Risk in Communities study (ARIC visit 5) and UK Biobank (UKB). CHIP (variant allele frequency [VAF] $\geq 2\%$) and large CHIP (VAF $\geq 10\%$) were ascertained using peripheral blood ES. The top three CHIP driver genes (DNMT3A, TET2, ASXL1) were studied individually. We measured inflammatory and cardiac biomarkers, including high-sensitivity CRP, interleukin-6 (IL6), IL18, high-sensitivity troponins T and I (hs-TnT, hs-TnI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and echocardiographic indices in ARIC.

Results: In ARIC participants (n=4131, mean $\pm$ SD age 76 $\pm$ 5 years, 41% male, 23% Black), 25% had CHIP, and 11.6% had large CHIP. In UKB participants (n=195,851, mean $\pm$ SD age 56 $\pm$ 8 years, 45% male, 1.9% Black), 5.8% had CHIP, and 2.6% had large CHIP. Meta-analyzed hazard ratios (95% confidence intervals) for AF were 1.12 (1.01–1.25, P=.036) for participants with vs. without large CHIP, 1.29 (1.05–1.59, P=.015) for with vs. without large TET2 CHIP, and 1.45 (1.02–2.07, P=.040) for with vs. without large ASXL1 CHIP. Large TET2 CHIP was associated with higher IL-6 levels. Additionally, large ASXL1 was associated with higher hs-TnT and increased left ventricular mass index.

Conclusions: Large TET2 and ASXL1, but not DNMT3A, CHIP was associated with higher IL-6 levels, indices of cardiac remodeling, and increased risk for AF. Future research is needed to elaborate on the mechanisms driving the associations and to investigate potential interventions to reduce the risk.

ABSTRACTS

Poster Number 63
Clinical Fellow/Resident
Aortopathy and Valvular Heart Disease

EVALUATING THE ASSOCIATIONS BETWEEN MEDICATIONS AND AORTIC GROWTH IN CHILDREN WITH BICUSPID AORTIC VALVE

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Background: Children with bicuspid aortic valve (BAV) often have progressive aortic dilation, which confers an increased risk of aortic dissection in adulthood. Data describing the effects associated with medication use and aortic dilation in children with BAV are limited. This study aimed to evaluate longitudinal trends of aortic growth, comparing those on angiotensin receptor blockers (ARBs) or beta-blockers (BBs) to no medical therapy.

Materials/Methods: This cohort included children with BAV <18 years from 2010-2023 with >1 echocardiogram with root or ascending z-score > 3.5 and >2 available echocardiograms. The primary exposure was dichotomized medication status. Medication status was further stratified as either none, ARB, BB, or dual therapy. The outcome evaluated was the trend in ascending aortic z-scores over time using multivariable mixed-effects linear regression to account for changing medication regimens over time, controlling for baseline z-score.

Results: In total, 278 patients (74% male) with 1,682 echocardiograms were included; 98 patients (35%) were on medications at some point during the period of interest (21% ever on ARBs, 16% on BBs, and 6% on dual therapy). On multivariable analyses, ascending aortic z-score reduced in patients on BBs relative to those not on medication (BB: -0.02/y + 0.040; no meds: +0.08/y + 0.01, p=0.018). The rates of change on ARBs (+0.13/y + 0.04, p=0.18) and dual therapy (+0.12/y + 0.06, p=0.13) were not significantly different than in patients on no medications.

Conclusions: In this cohort of children with BAV and aortic dilation, BB use demonstrated a reduction in the ascending aorta z-score relative to patients not on medications. This evaluation was limited by lower statistical power, as the number of treated patients in each subgroup was relatively small. However, this is the largest study to date evaluating the effect of medication on aortic dimensions over time in children with BAV.

ABSTRACTS

Poster Number 64
Clinical Fellow/Resident
Heart Failure and Cardiomyopathy

CARDIAC PULMONARY NERVE STIMULATION: A SINGLE-CENTER EXPERIENCE

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Background: The Cardiac Pulmonary Nerve Stimulation (CPNS) System is a neuromodulation device designed for endovascular stimulation of the cardiac autonomic nerves in the right pulmonary artery (RPA), aiming to augment left ventricular (LV) contractility in those with acute decompensated heart failure (ADHF).

Materials/Methods: In four subjects with ADHF, the neuromodulation stimulation (CN2) catheter was percutaneously delivered via the right internal jugular vein through a 16-French sheath to reach the treatment site in the RPA. Endovascular stimulation was applied alongside the conventional standard of care, which included loop diuretics. Therapy was administered for 48-96 hours, after which the CN2 catheter was removed.

Results: Four subjects successfully underwent CPNS implantation at Baylor St. Luke's Medical Center. The average duration for device implantation and explantation was 183 minutes and 24 minutes, respectively. The average duration of CPNS therapy was 3.25 days. All participants demonstrated improvements in key clinical indicators, including urine output, mixed venous oxygen saturation, NT-Pro BNP, and dyspnea scores. Notably, there were no serious complications during the procedures or while undergoing stimulation therapy.

Conclusions: Endovascular neuromodulation stimulation in the RPA holds promise as a viable option for treating ADHF, potentially reducing the need for inotropic agents and consequently lowering associated risks. Preliminary studies indicate that CPNS therapy can augment LV contractility while having minimal impact on myocardial oxygen consumption or heart rate.

ABSTRACTS

Poster Number 65
Clinical Fellow/Resident
Aortopathy and Valvular Heart Disease

CONTEMPORARY EXPERIENCE WITH THE USE OR REPAIR OF HOMOGRAFT ROOTS IN 130 PROXIMAL AORTIC REPAIRS

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Background: Aortic repair using homografts is uncommon, and its durability uncertain. We reviewed our experience with valved-homograft repair and revision of failed homografts to better understand its use and durability.

Materials/Methods: From 1994-2022, we performed 130 repairs that included 97 primary aortic root replacements using a valved homograft and with an additional 33 repairs of degenerated aortic root homografts. Infection necessitated initial homograft replacement in 71 (54.6%) interventions. Repair of degenerated root homografts was indicated by aortic valve dysfunction and other factors. Kaplan-Meier analysis was used to estimate survival; competing risk analysis assessed the risk of homograft failure, adjusted for death.

Results: Of the 97 primary homografts (median age 56 [IQR: 39-63]), all replaced the aortic root and varying portions of the ascending aorta; 36 (37.1%) replaced the ascending aorta or arch. Of 33 revisions of degenerated homografts, the homograft root was preserved using transcatheter (n=6; 18.2%) or open approaches (n=10; 30.3%), and in 17 (51.5%) the homograft root was fully replaced. Overall, there were 22/130 (17%) early deaths, with 18/97 (19%) after initial homograft ARR and 4/33 (12%) after homograft revision; the 5-year survival was 55.6 ± 10.6%. For 97 primary root homografts, after adjusting for death, the 5-year and 15-year cumulative incidence of homograft failure was 4.16 % and 14.58%.

Conclusions: Homografts are typically reserved for complex aortic repair (eg, infection often involving redo sternotomy). 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.

ABSTRACTS

Poster Number 66
Clinical Fellow/Resident
Aortopathy and Valvular Heart Disease

REOPERATION AFTER PRIOR AORTIC ROOT REPLACEMENT: EVOLUTION OF TECHNIQUE OVER 30 YEARS

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Background: Aortic root replacement (ARR) with a valve-replacing mechanical valve conduit is the cornerstone for treating aortic root aneurysm. However, the durability of ARR may be compromised and failure of the valve or root complex can necessitate late repair in some patients. We describe our experience with reoperation in patients with prior ARR, emphasizing indications for reintervention, types of subsequent repair, and outcomes of reoperative repair.

Materials/Methods: In a retrospective analysis of patients undergoing elective reoperative ARR between 1991 and 2023, 193 patients were identified. Patients were divided into three intervention subgroups: true redo ARR (n=132), surgical aortic valve replacement (SAVR; n=40), and transcatheter aortic valve replacement (TAVR; n=21).

Results: The median patient age was 54 years (range, 41-62). Few significant differences in baseline demographics were seen among the subgroups. Indications for reintervention included prosthetic valve regurgitation (94/193), pseudoaneurysm (55/193), and graft infection (46/193). Prior ARR techniques included a mechanical composite valve graft (CVG) in 74 patients, of which 71 underwent a subsequent redo ARR. Overall operative mortality was 14%, which differed with the approach to repair. The length of overall hospital stay was lower after TAVR (3 days [2-4.5]) compared to after true redo ARR (10 days [7-16]) and SAVR (10 days [7-20]; p<0.001). In late events, survival differed by approach (p=0.003) with 5-year survival 100% after TAVR, and at 10 years, was 48%±6% and 68%±10% after true redo ARR and SAVR, respectively.

Conclusions: The approach to reintervention after prior ARR is dictated by the indication for repair. Operative mortality trended higher with true redo ARR than with SAVR, which is not unexpected given the technical demands of redo aortic root intervention. When suitable, emerging TAVR techniques are beneficial to avoid redo sternotomy, with minimal operative mortality and a short length of stay.

ABSTRACTS

Poster Number 67
Clinical Fellow/Resident
Aortopathy and Valvular Heart Disease

UTILIZING HYPEROXYGENATED BLOOD DURING LEFT HEART BYPASS FOR THORACOABDOMINAL AORTIC ANEURYSM REPAIRS TO REDUCE POSTOPERATIVE RENAL DYSFUNCTION

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Background: Renal dysfunction after thoracoabdominal aortic aneurysm (TAAA) repair remains a significant and common complication despite improvements in renal perfusion methods, surgical technique, and perioperative care. With the aim to reduce renal dysfunction rates after TAAA repair, we tested a novel technique of using hyperoxygenated blood to perfuse the downstream aorta with selective visceral perfusion during repair.

Materials/Methods: Between February and December 2023, we provided intraoperative hyperoxygenated blood to 11 patients undergoing TAAA repair by adding an oxygenator to our left heart bypass (LHB) circuit. Separate return lines with perfusion catheters provided hyperoxygenated blood to the celiac trunk, superior mesenteric artery, and bilateral renal arteries as part of selective visceral perfusion. No additional cold blood or perfusate was administered. Postoperative complications including renal dysfunction were evaluated.

Results: Among the patients (age range 37-77 years), baseline preoperative creatinine level was 0.86-3.34 mg/dL and eGFR was 24-111 mL/min/1.73m²; 2 patients had non-dialysis-dependent chronic kidney disease at baseline. All patients received selective visceral perfusion and LHB during repair. Of the 11 patients, only 1 developed postoperative acute renal dysfunction (with creatinine elevation greater than 50% above baseline creatinine level within 10 operative days) but did not need dialysis. None of the patients had persistent renal failure on discharge.

Conclusions: This preliminary work suggests that using LHB with hyperoxygenated blood for selective visceral perfusion during TAAA repair produces favorable results, even for patients with baseline chronic renal dysfunction. Future steps include conducting a formal clinical trial of hyperoxygenated blood as an LHB perfusate in patients undergoing TAAA repair. LHB with hyperoxygenated blood should also be evaluated as a potential method to reduce spinal cord deficits and pulmonary complications in these patients.

ABSTRACTS

Poster Number 68
Clinical Fellow/Resident
Cardiogenic Shock

EVALUATION OF PROGNOSTIC FACTORS FOR MECHANICAL CIRCULATORY SUPPORT USING THE IMPELLA DEVICE AMONG PATIENTS WITH CARDIOGENIC SHOCK FROM MYOCARDIAL INFARCTION

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Background: In recent years, mechanical circulatory support devices have emerged as valuable tools in managing cardiogenic shock. Of these, the Impella system, which is a micro-axial, continuous-flow pump placed into the left ventricle, has gained increasing attention for its unique ability to provide percutaneous left ventricular unloading. Despite its novelty, however, availability of clinical evidence regarding the use of the Impella device is limited and predominantly derived from small clinical trials or registries. In this retrospective, observational study we aim to add to this limited body of knowledge by investigating what factors can predict survival in such a setting. Our primary hypothesis is that earlier initiation of mechanical circulatory support with the Impella device will increase survival to discharge.

Materials/Methods: 53 patients with cardiogenic shock resulting from myocardial infarction who received mechanical circulatory support with the Impella device were retrospectively evaluated using the Northwest Texas Healthcare System (NWTHS) Cerner electronic medical records database from February 2016 to October 2022. All patients were treated at Northwest Texas Hospital, Amarillo, TX. Survival to discharge and 30-day readmission rates were chosen as our outcomes of interest. Kaplan- Meier curves were used to analyze periprocedural time variables. All statistical analyses were performed using IBM SPSS 28.0 (SPSS Inc. Chicago, Illinois).

Results: Of the 53 patients, 27 or ~51% survived to discharge. Analysis of periprocedural time variables using kaplan-meier curves showed that survival decreased as length of time it took to receive an impella increased. The time needed to receive percutaneous coronary intervention (PCI) was also inversely correlated with survival. Longer duration of impella use was also correlated with decreased survival.

Conclusions: Analysis of the data suggests early intervention with the Impella device is associated with increased survival, confirming our hypothesis.

ABSTRACTS

Poster Number 69
Clinical Fellow/Resident
Arrhythmias and Channelopathies

A CASE OF SHORT QT SYNDROME IN AN ADOLESCENT MALE

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Background: Short QT syndrome (SQTS) is an autosomal dominant disease with a high risk of sudden death. Because of its rarity, SQTS may not be considered after an aborted arrest. Making it an even more challenging to diagnose, automated ECGs do not report short QTc. Lastly, most genetic testing companies do not test all causative SQTS genes. We report a teenager with SQTS due to SLC4A3 and highlight important clinical details to avoid missing this diagnosis.

Materials/Methods: Clinical data on this patient was collected from the TCH electronic medical record.

Results: A 17-year old healthy male presented after a cardiac arrest while standing. He was resuscitated out of ventricular fibrillation by emergency responders. Post-arrest work up the day of arrest revealed a normal ECG. He had a structurally normal heart with normal function. He had no subsequent arrhythmias during his inpatient stay. Repeat ECGs revealed QTc of 364msec and 384msec. His family history was significant for sudden death in his mother at age 31. An ICD was implanted and whole exome sequencing (WES) was sent which identified a heterozygous likely pathogenic variant in SLC4A3. Cascade testing resulted in the diagnosis in his maternal grandmother, sister, and younger brother, the latter of whom underwent ICD implant.

Conclusions: This case highlights important factors to consider in SQTS diagnosis. First, the ECG was initially normal after arrest. The QTc is almost uniformly prolonged after an arrest and hence this could have been the first clue that the underlying QTc was short. The automated ECG did not report a short QTc even though his shortest QTc was 364msec. Normal QTc cut off for SQTS is 340msec. SLC4A3 related SQTS is due to defect in a sodium bicarbonate channel and the QTc is short but longer than typical SQTS. Lastly, when considering genetic testing for SQTS, most current commercial tests do not test for SLC4A. If not specifically considered, the diagnosis of SLC4A3 SQTS would be missed.

ABSTRACTS

Poster Number 70
Junior Faculty
CAD, Atherosclerosis, Ischemia

BONE MORPHOGENETIC PROTEIN-BINDING ENDOTHELIAL REGULATOR REGULATES LIPOLYSIS

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Background: The vascular endothelium coordinates the delivery of endocrine hormones and small molecules to target tissues. Yet, how specific endothelial cell (EC) factors exert impacts in metabolic tissues remains undefined. Bone morphogenetic protein (BMP)-binding endothelial regulator (BMPER) is a circulating factor initially identified as an essential regulator of vascular development in a tissue and stage-dependent manner. Genetic studies identified strong association between human BMPER gene variants and its circulating abundance with obesity parameters. However, the roles of BMPER in obesity and lipid homeostasis remain unexplored.

Materials/Methods: When compared to their wildtype (WT) littermate counterparts, mice with global BMPER depletion (BC-KO) exhibited increased fat mass and adipocyte hypertrophy and elevated triglyceride (TG) contents.

Results: Ex vivo and in vitro studies revealed that BMPER promoted lipolysis in white adipose tissue (WAT) and induced the expression of lipid-regulating genes. Our data showed a significant reduction in Adipose triglyceride lipase (ATGL) expression levels in the white adipose tissue (WAT) of BC-KO mice when compared to their littermate controls. Mechanistically, our ChIP-Seq results demonstrated potential binding sites for Peroxisome proliferator-activated receptor alpha (PPAR α) within the mouse *bmp* promoter, and BMPER induction in the liver was found to be promoted by PPAR α . Moreover, BMPER expression level in liver and serum was dramatically induced by fasting, which can be abrogated by endothelial specific knock out PPAR α .

Conclusions: These results provide mechanistic evidence to suggest that fasting induces BMPER via PPAR α in the liver, which in turn regulates lipolysis in WAT. This discovery suggests that a new endocrine circuit from liver to adipose tissue in the regulation of energy homeostasis and offer new insights into whether BMPER may serve as a new therapeutic target for addressing obesity and other metabolic disorders.

ABSTRACTS

Poster Number 71
Junior Faculty
Congenital Developmental Heart Disease

B1 INTEGRINS REGULATE CELLULAR BEHAVIOR AND CARDIOMYOCYTE ORGANIZATION DURING VENTRICULAR WALL FORMATION

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Background: Cardiomyocytes interact with the extracellular matrix (ECM) through integrins, yet the mechanisms governing tissue architecture formation in the heart remain unclear. Integrins, serving as primary receptors, facilitate signaling pathways crucial for cell functions. We found that the $\beta 1$ integrin subunit ($\beta 1$), encoded by *Itgb1*, is highly expressed in all cardiac cell types. We hypothesize that $\beta 1$ integrins play a crucial role in regulating cardiomyocyte behavior and organization during ventricular wall morphogenesis in mice.

Materials/Methods: We applied mRNA deep sequencing and immunostaining to determine the expression of α/β integrins and their ligands in the embryonic heart. *Itgb1* was deleted via *Nkx2.5Cre/+* to generate myocardial-specific *Itgb1* knockout (B1KO) mice. A mosaic clonal lineage tracing system using the *Rosa26CreERT2* (iCre) mouse line coupled with whole embryo clearing was used to analyze individual clones at single-cell levels.

Results: $\beta 1$ and some of its ligands are asymmetrically distributed to the luminal side of cardiomyocytes, and fibronectin surrounds cardiomyocytes, creating a network for them. B1KO hearts lack a trabecular zone but a thicker compact zone. Fibronectin, a ligand of $\beta 1$, was absent in the myocardium of B1KO hearts. Furthermore, B1KO cardiomyocytes display a random cellular orientation and fail to undergo perpendicular cell division, be properly organized, and establish the proper tissue architecture to form trabeculae.

Conclusions: $\beta 1$ is asymmetrically localized in the cardiomyocytes, and some of its ECM ligands are enriched along the luminal side of the myocardium, fibronectin surrounds cardiomyocytes. $\beta 1$ integrins are crucial for cardiomyocytes to attach to the ECM, providing structural support for shape maintenance, perpendicular division, and cellular organization. Deletion of *Itgb1* results in the loss of $\beta 1$ and fibronectin, preventing cardiomyocytes from engaging with the ECM network and leading to failure in tissue architecture formation and trabeculae development.

ABSTRACTS

Poster Number 72
Junior Faculty
Coronary Artery Disease and Atherosclerosis

CANONICAL AND NONCANONICAL HEAT SHOCK FACTOR 1 (HSF1) SIGNALING DRIVE ATHEROSCLEROSIS

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Background: Smooth muscle cells (SMCs) in atherosclerotic lesions reduce expression of their characteristic contractile genes, migrate from the aortic medial layer to the intima, proliferate, and increase levels of cellular markers typically expressed by macrophages, fibroblasts, osteogenic cells and stem cells in an heterogenous manner. This phenotypic modulation of SMCs is partly driven by cholesterol-induced endoplasmic reticulum (ER) stress, and in particular PERK signaling, evident from SMC-specific deletion of Perk in hypercholesterolemic (HC) mice reducing plaque burden by 70%. We previously demonstrated that the augmented atherosclerosis in HC mice associated with either an SMC α -actin missense variant or SMC-specific deletion of pericentrin, is due to both genetic alterations inducing SMC cytosolic stress and subsequently activating of heat shock factor 1 (HSF1) signaling. This “canonical” HSF1 signaling augments atherosclerosis by increasing HMG-CoA reductase (a rate limiting enzyme in cholesterol biosynthesis) activity, and intracellular cholesterol levels, resulting in ER stress, PERK activation and enhanced SMC phenotypic modulation.

Materials/Methods: Using cell biological and whole animal studies, we further investigated the role of HSF1 in atherosclerosis.

Results: Interestingly, when wildtype SMCs are exposed to high levels of exogenous cholesterol in culture, they activate both PERK and HSF1, and inhibition of PERK signaling prevents HSF1 activation, suggesting novel “noncanonical” HSF1 signaling. Mechanistically, PERK inhibition blocks the activating phosphorylation of HSF1 by mTORC1. SMC-specific deficiency of Hsf1 leads to a 67% reduction in plaque size (N=12, males only, $p < 0.0001$) in the whole aortas of HC mice, compared to similarly treated wildtype littermates.

Conclusions: These data suggest distinct roles of canonical HSF1 signaling through increased cholesterol biosynthesis, and noncanonical HSF1 signaling by PERK-mTOR, both of which promote SMC phenotypic modulation and atherosclerosis.

ABSTRACTS

Poster Number 73
Junior Faculty
Heart Failure and Cardiomyopathy

EVALUATION OF LARGE ANIMAL MODELS WITH HFPEF THROUGH ECHOCARDIOGRAPHY

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Background: Heart Failure with Preserved Ejection Fraction (HFpEF) poses public health challenges due to its high morbidity and mortality rates. Despite extensive research efforts, the pathophysiology of HFpEF remains incompletely understood, necessitating innovative approaches for comprehensive investigation. Our study addresses this critical gap by developing a swine model that faithfully recapitulates key aspects of HFpEF pathogenesis, offering new insights into its complex mechanisms.

Materials/Methods: We simulated the broad etiological spectrum of HFpEF in swine, utilizing state-of-the-art tools for cardiac function assessment. This included thorough evaluation of crucial HFpEF echocardiographic parameters, continuous left ventricular (LV) pressure monitoring via interventional catheters, and systematic biomarker analysis to ensure the model's fidelity in mirroring human HFpEF.

Results: Our model effectively mimicked HFpEF, demonstrating preserved ejection fraction (EF) alongside notable signs of LV diastolic dysfunction and morphological changes. Increased E/e' ratios and Tricuspid Regurgitation velocities confirmed elevated LV filling pressures and diastolic dysfunction. Additionally, we observed reduced LV Global Longitudinal Strain (GLS) and early mitral annular velocity (e') indicating early systolic functional impairment, particularly under stress conditions. Observable left atrial (LA) enlargement reflected the middle stage of the modeled disease, closely mirroring HFpEF diagnostics.

Conclusions: In conclusion, our pioneering swine model not only provides a valuable platform for dissecting the intricate pathophysiology of HFpEF but also holds promise for accelerating the discovery of novel therapeutic interventions. By bridging the gap between preclinical research and clinical practice, our findings have the potential to revolutionize HFpEF management strategies, ultimately improving patient outcomes and reducing the global burden of this debilitating condition.

ABSTRACTS

Poster Number 74
Junior Faculty
Aortopathy and Valvular Heart Disease

EPIGENETIC REGULATION OF ADAPTIVE GENES MEDIATED BY TGF-BETA AND MEF2C IN VSMCS DURING AORTIC DISEASE PROGRESSION

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Background: Our recent studies have indicated smooth muscle cells (SMCs) transition from a contractile phenotype to ECM-producing SMCs in ascending thoracic aortic aneurysms (ATAA) patients, while they shift towards inflammatory SMCs in ascending thoracic aortic dissection (ATAD) patients. This transition represents an adaptive response in ATAA and a decompensatory status in ATAD. Here, we aim to elucidate the regulatory mechanisms underlying this adaptive response in SMCs.

Materials/Methods: We utilized NicheNet analysis of single-cell RNA sequencing (scRNA-seq) data from human aortic tissues to identify upstream signaling pathways regulating adaptive genes. Additionally, scRNA-seq analyses were performed on SMC-specific *Tgfb2*^{-/-} mice to assess the role of TGF-beta signaling in the adaptive response. Single-cell Assay for Transposase-Accessible Chromatin sequencing (scATAC-seq) was conducted on ascending aortic tissues from mice infused with angiotensin II (AngII) to explore the epigenetic control of the adaptive response. Co-immunoprecipitation (Co-IP) assays were employed to identify transcription factors (TFs) interacting with chromatin remodelers.

Results: NicheNet analysis suggested that TGF-beta signaling regulates adaptive genes in SMCs. SMC-specific *Tgfb2*^{-/-} mice exhibited impaired transition to an ECM-producing phenotype. Furthermore, NicheNet analyses indicated that TGF-beta may regulate adaptive genes through a variety of TFs such as MEF2C, in addition to SMADs. The scATAC-seq data supported the role of MEF2C in regulating adaptive genes through epigenetic mechanisms. MEF2C⁺ SMCs, but not MEF2C⁻ SMCs, demonstrated the ability to transition towards ECM-producing SMCs. Finally, Co-IP experiments revealed an interaction between MEF2C and the SWI/SNF complex subunit BRG1.

Conclusions: Our study unveils that TGF-beta-MEF2C- SWI/SNF signaling promotes the adaptive response through epigenetic regulation in SMCs of the ascending aorta.

ABSTRACTS

Poster Number 75
Junior Faculty
Aortopathy and Valvular Heart Disease

NON-CANONICAL SPLICE VARIANTS IN GENES FOR THORACIC AORTIC DISEASE ARE ENRICHED IN ACUTE THORACIC AORTIC DISSECTION CASES AND MARFAN SYNDROME FAMILIES WITH NEGATIVE PANEL TESTING

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Background: Individuals with heritable thoracic aortic disease (HTAD) are at significantly increased risk of deadly aortic dissections. Yet, genetic testing is positive in only 25% of affected individuals with a family history of disease and 10% of those without syndromic features or a familial component. Here, we characterize the role of non-canonical variants predicted to alter splicing (NCVAS) in thoracic aortic disease (TAD).

Materials/Methods: Using SpliceAI, NCVAS in COL3A1, FBN1, LOX, MYLK, SMAD3, and TGFB2 were assessed from exome sequencing (ES) of unsolved early-onset sporadic dissection (ESTAD) cases (n=551), HTAD family probands (n=437), and controls (n=1439), as well as clinical panel testing of sporadic dissection patients (n=2), and whole genome sequencing (WGS) from 57 HTAD pedigrees, including two families with Marfan syndrome (MFS) and negative genetic testing. Validation was performed in the Penn Medicine BioBank (PMBB) and UK Biobank (UKB).

Results: Six NCVAS were identified, exclusively in the ESTAD cohort (p=0.00045), with two more found on clinical testing. Despite no prior genetic diagnosis, these variants occurred in syndromic HTAD genes (FBN1, SMAD3, COL3A1) and showed reduced penetrance of TAD on segregation. WGS identified intronic NCVAS in FBN1 in two MFS families. PMBB and UKB validation cohorts showed a similarly increased NCVAS enrichment in genes for HTAD among dissection cases.

Conclusions: NCVAS may be an underrecognized contributor to TAD, particularly for sporadic dissection and unsolved MFS cases. Advanced splice prediction tools show promise in identifying previously excluded potentially disease-causing variants.

ABSTRACTS

Poster Number 76
Junior Faculty
Heart Failure and Cardiomyopathy

ACTIVATION OF A GPCR, ORL1 RECEPTOR: A NOVEL THERAPY TO PREVENT HEART FAILURE PROGRESSION

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Background: The number of ischemic heart failure (HF) patients is growing dramatically worldwide. However, there are at present no preventive treatments for HF. Our previous study showed that Gata4 overexpression improved cardiac function after myocardial infarction in the rat heart. In vitro RNAseq experiment with cardiac fibroblasts revealed that Gata4 overexpression significantly increased a Pnoc gene expression, an endogenous ligand for a GPCR, ORL1 receptor. We hypothesized that an activation of ORL1 receptor would suppress HF in a rat ischemic heart model.

Materials/Methods: Adult Sprague Dawley rats (8 weeks old, 6 males and 6 females) underwent left anterior descending coronary artery ligation. Three weeks later, normal saline or MCOPPB (ORL1 activator, 2.5mg/kg/day) intraperitoneal injection was started, and continued 5 days a week, for 3 months. Echocardiography was performed six times, pre-operative, 3 days after coronary artery ligation, pre-MCOPPB or saline injection, and 1, 2, and 3 months after saline or MCOPPB injection started. Animals were euthanized after 3 months follow up and the heart was harvested for histological analysis.

Results: Echocardiographic data showed that ejection fraction significantly improved in the MCOPPB group (MCOPPB vs saline at 2 months follow-up, 58 ± 3 vs 45 ± 2 , $p < 0.001$, MCOPPB vs saline at euthanasia, 67 ± 3 vs 43 ± 2 , $p < 0.001$). End-systolic volume was significantly decreased in MCOPPB- received group at euthanasia (MCOPPB vs saline, $140 \pm 30 \mu\text{L}$ vs $280 \pm 44 \mu\text{L}$, $p < 0.001$). Fibrosis area, stained by Masson-Trichrome, significantly decreased in MCOPPB group (% fibrosis area, MCOPPB vs saline, 14 ± 2 vs 29 ± 10 , $p < 0.05$). Angiogenesis was assessed by CD31 staining and MCOPPB group had significantly higher vessel counts in border zone (44 ± 12 vs 16 ± 4 , $p < 0.01$).

Conclusions: ORL1 receptor activator, MCOPPB, administration significantly improved cardiac function, reduced fibrosis and induced angiogenesis, resulting in attenuating HF.

ABSTRACTS

Poster Number 77
Junior Faculty
Aortopathy and Valvular Heart Disease

NANOPARTICLE CONTRAST-ENHANCED COMPUTED TOMOGRAPHY IN A BAPN-INDUCED MOUSE MODEL OF AORTIC ANEURYSM AND DISSECTION

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Background: Aortic aneurysm and dissection (AAD) is characterized by elastin fragmentation, loss of smooth muscle cells (SMCs) and endothelial dysfunction associated with enhanced endothelial permeability. In our previous work, we demonstrated that nanoparticle contrast-enhanced computed tomography (nCECT) enabled in vivo detection of enhanced endothelial permeability associated with early stages of aortic degeneration. In this work, we utilized nCECT to interrogate aortic endothelial permeability during AAD progression in a BAPN-induced mouse model of sporadic AAD.

Materials/Methods: C57BL/6J mice were challenged with BAPN, administered in drinking water, starting at postnatal day 21 (P21). Animals underwent nCECT imaging at P28, P35, P42 and P49 days (n=14- 16/time point). Liposomal iodine nanoparticle CT contrast agent (Lip-I) was administered (i.v.) 5 days prior to nCECT. CTA was performed after nCECT to localize nCECT findings to aortic anatomy. At the end of imaging, aortas were harvested for gross examination, ex vivo nCECT and histologic analysis. nCECT imaging findings were compared with gross examination findings of aortic pathology.

Results: nCECT demonstrated imaging findings of intramural signal enhancement as early as 1 week after start of BAPN treatment (P28). The incidence of nCECT findings and gross exam findings were 16% and 9% at P28, 39% and 29% at P35, 54% and 50% at P42, and 75% each at P49 respectively. A 100% concordance was seen between nCECT findings and gross observation of aortic pathology across all studied time points. Histologic analysis confirmed evidence of aortic degeneration at sites of nCECT findings.

Conclusions: nCECT detected enhanced endothelial permeability associated with aortic degeneration in a BAPN-induced mouse model of sporadic AAD.

ABSTRACTS

Poster Number 78
Junior Faculty
Heart Failure and Cardiomyopathy

ROLE OF JUNCTOPHILIN-2 (JPH2) IN REGULATING MITOCHONDRIAL FUNCTION AND OXIDATIVE STRESS IN CARDIOMYOPATHY

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Background: Heart failure impacts millions of individuals in the United States. At the cellular level, heart failure is characterized by contractile and metabolic dysfunction, leading to diminished cardiac output. Junctophilin-2 (JPH2), an inter-membrane protein, plays a crucial role in maintaining the precise spatial relationship between the plasmalemma and sarcoplasmic reticulum (SR) within 'junctional membrane complexes' (JMCs), thereby facilitating efficient excitation-contraction coupling. Emerging evidence suggests that JPH2 extends its influence on mitochondria, binding to mitofusin-2, a pivotal protein in SR- mitochondrial crosstalk highlighting an area yet to be fully explored.

Materials/Methods: Cardiac functionality was analyzed by echocardiography. For reactive oxygen species (ROS) levels, dihydroethidium dye was used to measure cytosolic ROS, and mitochondrial ROS levels were determined in isolated cardiomyocytes using mitoSox.

Results: Our studies revealed that mice carrying a missense variant (A399S) in JPH2, identified in hypertrophic cardiomyopathy (HCM) patients, develop pertinent HCM characteristics (septal thickness, 1.25 ± 0.04 mm in A399S, vs. 1.00 ± 0.01 mm in WT, $P < 0.001$), confirming a causal link. Furthermore, cardiomyocytes from the mutant mouse had compromised mitochondrial calcium retention capacity and diminished oxygen consumption rate (OCR). Additionally, JPH2 was identified in cardiac mitochondrial fractions. Next, elevated production of both cytoplasmic and mitochondrial reactive oxygen species (ROS) were observed in these mutant hearts. Unbiased proteomics revealed JPH2's interaction with peroxiredoxin 6 (PRDX6), a versatile antioxidant protein. Remarkably, restoring PRDX6 levels via AAV9- mediated gene therapy prevented cardiomyopathy progression in JPH2-A399S mice.

Conclusions: This research highlights JPH2's newly discovered roles in mitochondrial function and oxidative stress in cardiomyopathies, suggesting that in-depth mechanistic studies could pave the way for new treatments.