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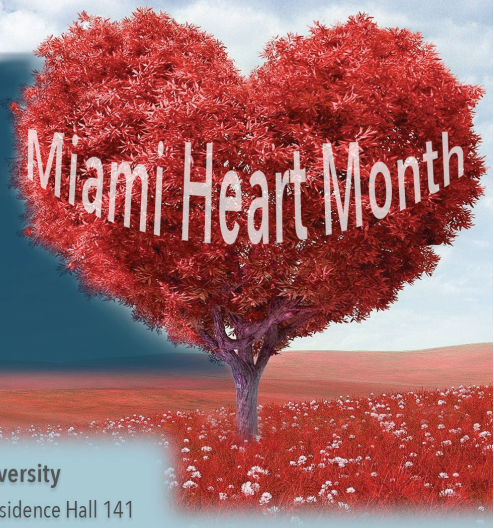
The Department of **BIOMEDICAL ENGINEERING**
presents

Heart Day Symposium

Friday, February 21, 2020

9:30am – 6:00pm

An event to bring awareness to cardiovascular diseases.



Florida International University
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Made possible by the FIU BME Wallace H. Coulter Foundation Lecture Series

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WELCOME

Joshua Hutcheson, Ph.D.
Assistant Professor

Sharan Ramaswamy, Ph.D.
Associate Professor

to FIU's third annual Miami Heart Day! With generous support from the Department of Biomedical Engineering W. H. Coulter Lecture Series at FIU, we established the Miami Heart Month to coincide with the American Heart Month recognized nationally by the AHA, CDC, and NHLBI. For three consecutive Fridays in February, we invite renowned investigators to Miami for a series of seminars focused on cardiovascular research. Two years ago, we hosted our inaugural Heart Day event, the capstone event of Miami Heart Month. The goal of the Heart Day Symposium was to gather cardiovascular researchers from across South Florida to learn from each other and discuss current research and lingering challenges in cardiovascular medicine. In the past two years, we have welcomed researchers from several departments within FIU, as well as researchers from University of Miami, Nova Southeastern University, Florida Atlantic University, Joe DiMaggio Children's Hospital, and Baptist Health South Florida. We are excited to continue this tradition for the third straight year, and we have developed an outstanding program.

This year, we are delighted to welcome Dr. Katherine Yutzey from Cincinnati Children's Hospital to deliver the morning's keynote lecture. Dr. Yutzey is a highly eminent scientist at the forefront of Cardiovascular disease and is particularly well-known for her work in uncovering molecular mechanisms that lead to heart valve disease. Following Dr. Yutzey's lecture, we will gather for lunch and a poster symposium that will highlight cutting edge cardiovascular research being performed in South Florida. Our afternoon keynote lecture will be delivered by Dr. Lina Shehadeh from the University of Miami School of Medicine. Dr. Shehadeh investigates microRNA-mediated mechanisms in cardiovascular diseases and is well-known for her work on Osteopontin in augmenting the risk for cardiac-related abnormalities. The day will be capped off by a moderated panel discussion on current challenges and the future of cardiovascular research and medicine. We are happy that you have decided to join us this year, and we hope that you will plan to join us again in February 2021!

Joshua Hutcheson, PhD

Sharan Ramaswamy, PhD, FAHA, FASME

AGENDA

9:30am - 10:30am
Seminar by Dr. Katherine Yutzey
Heart Valve Development and Disease Mechanisms
Dr. Yutzey is a highly-eminent scientist and an internationally recognized expert in delineating molecular mechanisms in heart valve development.

11:00am – 12:20pm
Poster symposium
Featuring cardiovascular research from across South Florida

12:30pm – 1:30pm
Lunch

2:00pm – 3:00pm
Seminar by Dr. Lina Shehadeh
Role of Osteopontin in Heart Failure with Preserved Ejection Fraction (HFpEF)
Dr. Shehadeh's laboratory is investigating the molecular mechanisms by which microRNAs regulate atherogenesis and stem cell differentiation. Her research has identified Osteopontin as a major regulator of heart failure and Alport pathology.

3:00pm – 4:00pm
Q&A panel session on the future of cardiovascular research and medicine

4:00pm – 6:00pm
Chocolate with the Chair hosted by FIU Biomedical Engineering Society

PRESENTERS

Dr. Katherine Yutzey
Cincinnati Children's Hospital Medical Center: Professor, UC Department of Pediatrics

Dr. Lina Shehadeh
University of Miami: Associate Professor: of Medicine Division of Cardiology

DR. KATHERINE YUTZEY

Cincinnati Children's Hospital Medical Center: Professor, UC Department of Pediatrics

KATHERINE E. YUTZEY, PHD, FAHA, FAAA, Professor of Pediatrics, Cincinnati Children's Hospital Medical Center. She has a BA in Biology from Oberlin College (1986), a PhD from Purdue (1992), and post-doctoral training in heart development. She joined CCHMC as Assistant Professor (1995) and was appointed Professor in 2007. Dr. Yutzey is the first recipient of the Schmidlapp Women Scholars Award and currently holds an endowed chair from the Cincinnati Children's Research Foundation. Her work is supported by NIH and the American Heart Association. Current areas of research include heart valve development and disease, including inflammation, and mechanisms of cardiomyocyte proliferation.

HEART VALVE DEVELOPMENT AND DISEASE MECHANISMS

ABSTRACT: Congenital heart valve malformations or developmental anomalies can lead to progressive valvular degeneration and dysfunction, necessitating replacement later in life. Myxomatous valve disease (MVD) is characterized by thickening of valve leaflets and increased proteoglycan accumulation, leading to prolapse and valvular insufficiency. Mouse models of MVD were used to identify critical contributions of valve and immune cell lineages, extracel-lular matrix (ECM) organization, and cell signaling to the initiation and progression of heart valve disease. Mice with the Marfan Syndrome Fibrillin1(FBN1) C1039G mutation exhibit mitral valve thickening, increased numbers of CD45+ leukocytes, and abnormal ECM remodeling within 2 months after birth. Interest-ingly, increased Wnt/beta-catenin signaling is detected in valve interstitial cells of the FBN1C1039G mice, along with increased numbers of CD45+ cells and cytokine signaling, at early stages of the disease. Moreover, increased numbers of CD45+ cells and macrophages are present in a pig Marfan syndrome model with myxomatous mitral valves, as well as in human MVD. In normal heart valves, CD45+ myeloid lineage cells are present at birth, and their numbers increase during post-natal heart valve remodeling. The majority of the valvular CD45+ cells are macrophages, as confirmed by flow and lineage tracing of Cx3Cr1 expressing cells. In MVD, CD45+ proinflammatory monocytes are increased prior to major ECM abnormalities. In Marfan syndrome mice, deficiency of circulating macrophages improves valve morphology and pre-vents ECM abnormalities. Thus targeting macrophages may be an effective strategy for development of new therapeutic approaches to preventing myxomatous disease progression.

DR. LINA SHEHADEH

University of Miami Miller School of Medicine: Associate Professor of Medicine

DR. LINA SHEHADEH The Shehadeh lab is focused on rare kidney disease, cardiovascular disease, Duchenne Muscular Dystrophy, and cardiac regeneration. The Shehadeh team investigates the role of Osteopontin (OPN) and its downstream effectors in a variety of small and large animal models. They utilize cutting-edge techniques such as antibody-, aptamer-, and AAV gene- therapy in surgical and genetic mouse models. They routinely use extracellular flux analysis, echocardiography, left ventricular catheterization , patient-derived iPSC differentiation, and a variety of biochemical assays to study cardiac/renal function, mitochondrial function and a variety of mechanistic studies.

ROLE OF OSTEOPONTIN IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)

ABSTRACT: Background: Patients with chronic kidney disease (CKD) and coincident heart failure with preserved ejection fraction (HFpEF) may constitute a distinct HFpEF phenotype. Osteopontin (OPN) is a biomarker of HFpEF and predictive of disease outcome. We recently reported that OPN blockade reversed hypertension, mitochondrial dysfunction and kidney failure in Col4a3-/- mice, a model of human Alport Syndrome. Objectives: Identify potential OPN targets in biopsies of HF patients, healthy controls and human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs). Characterize the cardiac phenotype of Col4a3-/- mice, relate this to HFpEF and investigate possible causative roles for OPN in driving the cardiomyopathy. Methods: 2-Oxoglutarate Dehydrogenase-Like (Ogdhl) mRNA and protein were quantified in myocardial samples from patients with HFpEF, HFrEF, and donor controls. OGDHL expression was quantified in hiPS-CMs treated ± anti-OPN antibody. Cardiac parameters were evaluated in Col4a3-/- mice ± global OPN knockout or AAV9-mediated delivery of Ogdhl to the heart. Results: Ogdhl mRNA and protein displayed abnormal abundances in cardiac biopsies of HFpEF compared with donor controls or HFrEF patients. Blockade of OPN in hiPS-CMs conferred increased OGDHL expression. Col4a3-/- mice demonstrated cardiomyopathy with similarities to HFpEF including diastolic dysfunction, cardiac hypertrophy and fibrosis, pulmonary edema, and impaired mito-chondrial function. The cardiomyopathy was ameliorated by Opn-/- coincident with improved renal function and increased expression of Ogdhl. Heart-specific overexpression of Ogdhl in Col4a3-/- mice also improved cardiac function and cardiomyocyte energy state. Conclusions: Col4a3-/- mice present a model of HFpEF secondary to CKD wherein OPN and OGDHL are intermediates, and possibly therapeutic targets.

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CELLULAR CONTRACTION IS REQUIRED FOR HYPERGLYCEMIA-INDUCED VASCULAR CALCIFICATION

Authors: Hooi Hooi Ng, Daniela Medina, Amirala Bakhshian Nik, Joshua D. Hutcheson

Abstract

Introduction: Diabetes-related cardiovascular disease is associated with the development of vascular calcification. Therapeutic intervention for the prevention or treatment of hyperglycemia-induced calcification is hindered by the lack of clarity in the fundamental mechanisms that lead to mineral formation in the vascular wall. Glucose increases smooth muscle cell (SMC) contractility, and studies in non-vascular cells show that elevated contractility is required for calcification. We hypothesized that abnormal cytoskeletal alteration and elevated cell contraction contribute to the calcification process in diabetes.

Methods and Results: Primary human coronary artery SMCs were cultured under three glucose concentrations (0, 1.5 g/L and 4.5 g/L) in normal media or osteogenic media for up to 21 days. After three days of culture in osteogenic media, SMCs in 1.5 g/L glucose and 4.5 g/L glucose showed a 26% and 42% reduction in cell area, respectively when compared to SMCs cultured in no glucose media, as assessed by phalloidin-staining of actin filaments. These data suggest that hyperglycemic conditions increase SMC contractility. The reduction in cell area corresponded to a dose-dependent increase in matrix mineralization, measured through Alizarin Red S staining, in SMCs cultured under osteogenic conditions for three weeks. Quantitative PCR analysis revealed the glucose-dependent increase in SMC calcification positively correlated with an upregulation of NADPH oxidase 4 (NOX4) mRNA expression, a key regulator of cytoskeletal reorganization in SMCs. SMCs also adopt an osteogenic phenotype in osteogenic media with increasing glucose concentrations as shown by an upregulation in osteonectin (SPARC) mRNA expression, a marker of osteoblast-like cells. The use of an actin-polymerizing agent, jasplakinolide, prevented the reduction in SMC area following three days of culture in 4.5 g/L glucose, and attenuated matrix mineralization after three weeks in culture.

Conclusions: Our data demonstrate that SMC contraction is required for calcification under hyperglycemic conditions. Future development of therapeutic agents that can inhibit cell contractility may serve as an attractive strategy to mitigate vascular calcification in diabetes.

HYDRODYNAMIC ASSESSMENT OF A SMALL INTESTINAL SUBMUCOSA TUBULAR VALVES

Authors: Chia-Pei, Denise Hsu, Asad Mirza, Robert Matheny, Joshua D. Hutcheson, Sharan Ramaswamy

Abstract

For children with critical valve defects and older patients who are contraindicated for receiving mechanical and bioprosthetic valves, treatment options are extremely limited. The purpose of this study is to determine whether tubular porcine small intestinal submucosa (PSIS) bio-scaffold valves can facilitate robust aortic and mitral valvular hydrodynamic functions and serve as potential treatment options. 26-mm PSIS tubular valves were sutured to a custom, 3D-printed valve holder along its ring and posts on the distal end. Three posts at 120 degrees apart were used for the aortic valve position, and two posts at 150 degrees apart were used for the mitral valve position. Hydrodynamic tests were performed using a pulse duplicator system filled with 0.9% saline solution. A flow probe was affixed between the aortic and ventricular chambers to measure the aortic outflow, and between the atrial and ventricular chambers to measure the mitral outflow. Three pressure transducers were inserted in the atrial, ventricular, and aortic locations. Tests utilized a stroke volume of 71.4 mL, 70 bpm, and an input flow waveform comprising of a 35% systolic-65% diastolic configuration. The tubular PSIS valves placed in both aortic and mitral positions appear to facilitate robust hydrodynamic valve function and may concomitantly serve as a scaffold for de novo valvular tissue growth by the host after implantation. Further studies involving seeding tubular PSIS valves with valvular cells and conditioning them in bioreactors will be conducted to assess the effects of both mechanical and biochemical stimuli on valve performance.

A METHOD TO QUANTIFY TENSILE BIAXIAL PROPERTIES OF MOUSE AORTIC VALVE LEAFLETS

Authors: Daniel Chaparro, Valentina Dargam, Paulina Alvarez, Jay Yeung, Ilyas Saytashev, Jenniffer Bustillo, Archana Loganathan, Jessica Ramella-Roman, Arvind Agarwal, Joshua D. Hutcheson

Abstract

The aortic valve (AV) has a highly organized extracellular matrix (ECM) in which orthogonally aligned collagen and elastin fibers promote proper valve function. Asymptomatic pathological remodeling of the ECM leads to improper valve function and ultimately AV disease. Various animal models are used to characterize and understand human AV disease. Large mammals are used to assess the relation between structural macromolecular ECM components and mechanical properties of the tissue elucidating the importance of these components in AV function. Smaller mammals are used in mechanistic studies as they can be genetically modified to recapitulate certain biological aspects of human AV disease. Combining mechanical strain regimen and biological mechanistic studies is a major obstacle for both large and small mammals since large mammals are expensive to genetically modify and small mammal tissues are difficult to mechanically test. Mouse aortic valve leaflet (MAVL) tensile properties have not been properly quantified due to their microscopic size. We developed a method in which the biaxial tensile properties of MAVL tissues can be assessed by adhering the tissues to a silicone rubber membrane. Applying equiaxial tensile loads on the tissues resulted in the characteristic orthotropic response of AV tissues seen in larger mammals. Our Data suggests that orthogonal directions in MAVL tissues are differ by ~155kPa in stiffness ($n=6$, $P=0.0006$). This method can be implemented in future studies involving mechanical stimulation of genetically modified MAVL tissues bridging the gap between biomolecular mechanisms and valve mechanics in mouse models of valve disease.

AORTIC VALVE ELASTOGENESIS REQUIRES NEURAL CREST DERIVED VALVULAR INTERSTITIAL CELLS

Authors: Sana Nasim, Beatriz Abdo Abujamra, Jorge Rubinos, Joshua D. Hutcheson, Lidia Kos

Abstract

The aortic valve (AoV) controls unidirectional blood distribution from the left ventricle of the heart to the aorta for systemic circulation. During the systolic and diastolic phases, AoV leaflets rely on a precise extracellular matrix (ECM) microarchitecture for appropriate biomechanical performance from collagen, elastin and glycosaminoglycans. The ECM structure is maintained by valvular interstitial cells (VICs), which reside within the leaflets. VICs are a heterogeneous population of cells that are derived from a mixture of developmental precursors. Mainly, VICs arise from endocardial and neural crest cells that migrate into the cardiac cushions during development. The contribution of these diverse populations to the formation of the ECM microarchitecture has not been established. Relatively little is known about regulation of elastin fibers, though elastin abnormalities result in congenital AoV defects and elastin degradation initiates AoV disease. To establish the timing of elastin (Eln) expression in the murine AoV, we performed RT-qPCR and found that Eln peaks at late stages of embryogenesis (E17.5) and decreases considerably postnatally but remains at low levels in adulthood. Two-D photon and confocal microscopy of AoVs from mutant mice revealed that elastin fibers were missing in Kitwv/wv mice that have no melanocytes and were more abundant and disoriented in Edn3 transgenic hyperpigmented mice. These results indicate that VICs with a melanocytic phenotype are required for proper elastin fiber patterning in the AoV. Additionally, we found that Tyrosinase positive VICs express alpha smooth muscle actin (aSMA) protein and elastin mRNA suggesting they are responsible for elastin production. Further understanding of the process of elastogenesis in the AoV will provide insights into AoV homeostasis and disease.

MECHANISTIC AND QUANTITATIVE ANALYSIS OF CALCIFIC EXTRACELLULAR VESICLE FORMATION IN MINERALIZATION

Authors: Jessica Molina, Amirala Bakhshiannik, Joshua D. Hutcheson

Abstract

Calcification, a leading contributor to cardiovascular disease, begins with the release of ~100 nm-sized extracellular vesicles (EVs) by resident vascular smooth muscle cells (VSMCs). Under pathological conditions, VSMCs undergo an osteogenic phenotypic change to osteoblast-like cells and release calcifying EVs. These calcifying EVs exist within larger populations of EVs released during normal cellular processes. It has been shown that calcific EVs originate in caveolae, flask-shape invaginations in plasma membrane. Previous studies on mesenchymal stem cells indicate that calcification requires elevated cell contractility. In VSMCs, increased contractility can occur through a mechanistic pathway that includes Src tyrosine kinase-induced activation of epidermal growth factor receptor (EGFR) within caveolae. The caveolae alterations result in RhoA protein kinase activity and subsequent VSMC contraction. In this study, we investigate the relevance of this pathway in calcifying EV formation from two cell types, which are responsible for physiological and pathological mineralization, osteoblasts and VSMCs, respectively. These cells were cultured in pro-calcific media and co-treated with either Src tyrosine kinase inhibitor, EGFR inhibitor, or RhoA protein kinase inhibitor. To characterize the released EVs, the media from these cultures was collected and analyzed for tissue non-specific alkaline phosphatase activity, an enzyme required for calcification. Furthermore, tunable resistive pulse sensing (TRPS) will be used to quantitively asses the properties of calcifying EVs released by osteoblasts and VSMCs. The use of TRPS can aid in the differentiation of unique calcifying EVs properties that contribute to disease and potentially lead to develop better treatment options through development of vesicle-specific therapies.

COMPLETE REGENERATION OF NEOCHORDAE COMPONENT OF BIO-SCAFFOLD MITRAL VALVE APPARATUS IN A NON-HUMAN PRIMATE MODEL

Authors: Brittany A. Gonzalez, Frank Scholl, Steven Bibevski, Krishna Rivas Wagner, Jennifer Bibevski, Lazaro Hernandez, Elena Ladich, Vincent Brehier, Mike Casares, Pablo Morales, Jesus Lopez, Joseph Wagner, Sharan Ramaswamy

Abstract

Congenital heart defects (CHDs) are the most common type of birth anomaly, affecting 8 out of 1,000 newborns; each year about 35,000 babies in the United States are born with these defects. CHDs occur when there is a problem with the structure of the heart at birth, or soon after. Critical congenital heart valve defects (CCHVDs) are a subset of CHDs, which account for ~25% of all CHD cases. Timely treatment plays a key role in CCHVDs. However, CCHVDs in newborns have very limited treatment options due to challenges associated with the unavailability of small-sized commercial valves and the inability of prosthetic valves to support somatic growth. To facilitate growth, we successfully implanted a bioscaffold valve comprising of porcine small intestinal submucosa (PSIS) in an animal model to assess de novo tissue formation over time post-implantation. Juvenile baboons (12-14 months, n=3) were implanted with a hand-made bicuspid tubular-shaped, PSIS (Cormatrix, Roswell, GA) valve in the mitral position. The PSIS valves were explanted at 11-month and 20-month post-implantation for histological assessment via hematoxylin and eosin (H&E) and Movat's Pentachrome (Movat's) staining via Alizée Pathology, Inc. manufacturing protocol. It was found that at both time points (11- and 20-month explants) that PSIS was able to regenerate neochordae, composed of collagen and proteoglycans. Our findings suggest that our PSIS bioscaffold can regenerate a neochordae and integrate well with the papillary muscle, as well as the left ventricle without any need to biochemical or biomechanical treatment or stimulation. Nonetheless, to enable a successful bio-scaffold mitral valve apparatus with regenerative capacities, it is important to assess other components of the PSIS mitral valve.

FLUID DYNAMICS ON A EDWARDS SAPIEN 3 STENT AND ITS IMPLICATIONS TO THROMBOSIS

Authors: Asad M. Mirza, Amanda Barreto, Sharan Ramaswamy

Abstract

Trans-aortic valve replacement (TAVR) procedures have become popular for treatment of calcified aortic valve disease (CAVD). However, this device is prone to thrombosis, leading to progression to stroke. It has been previously shown that flow stagnation, low wall shear stress (WSS), and high oscillatory shear stress (OSI) correlate with thrombosis formation. Our objective was to identify a link between blood flow pulsatility and risk for thrombosis, i.e., clot formation by examining the hemodynamic environment surrounding the stent of a commercially-available TAVR system SAPIEN 3. A 26 mm SAPIEN 3 stent geometry was modeled in Solidworks 2020. The stent was placed in a mimicked adult aortic geometry. Blood was assumed to be incompressible and its viscosity was defined using the non-Newtonian Carreau model. Two simulations (COMSOL Multiphysics with ANSYS Meshing) were done, one with a physiologically relevant aortic inlet flow profile and another with its average. For the aortic flow-case, peak velocity streamlines showed more disturbed flow surrounding the TAVR stent-region. The constant flow case was unidirectional with mild to no flow disturbances near the stent-struts. Overall, the TAWSS on the stent was low for the aortic flow-case, <4 dynes/cm2, and even lower for the constant flow case. Fluid-induced oscillatory shear stresses were found under the aortic pulsatile flow condition, but none were present for constant flow case. We report that blood pulsatility induces a high degree of temporal blood oscillations on TAVR stents-geometries-alone, specifically at the distal strut surfaces, potentially making these locations vulnerable to clot formation.

NADPH OXIDASE AND RHO KINASE MODULATE CAVEOLIN-1 RELEASE IN EXTRACELLULAR VESICLES FROM VASCULAR SMOOTH MUSCLE CELLS UNDER MECHANICAL STRETCH

Authors: Mohammad Shaver, Joshua D. Hutcheson

Abstract

Extracellular vesicles (EVs) mediate intercellular trafficking and arterial wall remodeling. Caveolin-1 (Cav-1), a structural component of caveolae, plays a critical role in biogenesis of a subset of EVs from vascular smooth muscle cells (VSMCs) and is required for vascular calcification. Caveolae buffer the plasma membrane to changes in mechanical tension and actively participate in mechanotransduction. However, the effect of mechanical stretch on Cav-1-dependent EV formation in VSMCs remains unknown. In this study, porcine VSMCs were cultured under cyclic stretch (10%, 0.5Hz) for 72hrs. Western blotting showed a redistribution of Cav-1 into EVs (100±25% increase in the ratio of EV Cav-1 to intracellular Cav-1 for stretched VSMCs compared to non-stretched VSMCs) and a 55.1% reduction in s mooth muscle alpha-actin in stretched VSMCs compared to non-stretched VSMCs. In order to investigate the role of the actin cytoskeleton in the stretch-induced Cav-1 trafficking, we inhibited Rho kinase (10μM Y-27632) and Nox1/4 (10μM GKT137831), mediators of VSMC actin filament dynamics. Compared to non-treated stretched samples, VSMCs under stretch treated with either inhibitor exhibited a further increase in Cav-1 redistribution to EVs (159±38% and 60±15% increase in EV Cav-1/intracellular Cav-1 for Rho kinase inhibitor and NOX1/4 inhibitor, respectively, compared to VSMCs under stretch with no inhibitors). Immunofluorescence staining showed that both inhibitors reduced actin filaments and resulted in Cav-1 internalization within the VSMCs. Alterations in VSMC actin results in Cav-1 intracellular trafficking and EV release. These data provide new insight into the effect of mechanical stimulation on EV formation.

CORRELATING AORTIC VALVE STRUCTURE TO HEART SOUND CHARACTERISTICS

Authors: Valentina Dargam, Amirala Bakhshian Nik, Joshua D. Hutcheson

Abstract

Aortic valve disease (AVD) occurs when aortic valve leaflets become thickened and stiff due to fibrotic remodeling and formation of calcific nodules. AVD is the most common valve disease and patients may experience no symptoms until the disease has progressed significantly. Asymptomatic patients are not referred to specialists for advanced imaging procedures that can diagnose AVD. Better screening strategies that can be implemented into routine physical examinations are needed to detect AVD, regardless of symptom manifestation. The vibrations of aortic valve leaflets during valve closure produce the audible frequencies heard through a doctor's stethoscope. In this study, we hypothesize that microstructural alterations during aortic valve remodeling cause changes in the valvular acoustic characteristics prior to gross changes in valve performance. Starting at 10-weeks of age, 8 ApoE-KO mice were fed an atherogenic diet and heart sounds were recorded weekly. At 35-weeks of age, the mice were sacrificed for analysis of mineral growth. Preliminary results show changes over the course of the experiment in both the time and frequency domains. The dominant frequency of the S2 sound increases as early as 15 weeks, at early stages of valve remodeling prior to changes in valve performance. Principle component analysis shows that the first principle component segregates heart sounds associated with time points prior to valve remodeling, early remodeling with preserved valve function, and late stages with altered valve function. The outcomes of the proposed research can contribute to the future development of a non-invasive diagnostic tool to identify patients with different stages of AVD.

TOWARDS HOMOGENIZED CONSTITUTIVE CHARACTERIZATION OF SEVERELY CALCIFIED AORTIC VALVE LEAFLETS

Authors: Amanda Barreto, Asad M. Mirza, Pranjal Nautiyal, Darryl Dickerson, Joshua D. Hutcheson, Arvind Agarwal, Sharan Ramaswamy

Abstract

Aortic valve disease (AVD), a health condition which requires prosthetic valve replacement, is expected to increase from 2.5 million cases in 2000 to 4.5 million in 2030 worldwide. It is usually manifested as aortic valve stenosis, which is associated with thickening and calcification of the leaflets and leads to narrowing of the valve and thus reducing blood flow. With the current growing technological advancements, transcatheter aortic valve replacement (TAVR) has become the safer treatment for patients who are at high risk of undergoing an open-heart surgery. The current study aims to understand the etiology of calcified plaque distribution in diseased aortic valve leaflets in terms of their constitutive properties. Subsequently, if these properties can be homogenized, the resulting stress-strain relationship can be used in predictive computational models of blood flow through commercial TAVR systems in a patient-specific manner. In so doing, the interaction in the flow with the surround calcified plaque geometry can identify potential complications post-TAVR, such as clots due to flow stagnation. Here, as a first attempt, porcine aortic valve leaflets will be collected from a local abattoir and transported to the laboratory in cold phosphate buffered saline solution (PBS). Then mechanical testing will be done using a soft tissue nanoindenter that measures stress and strain properties. Once approaches have been validated we will then repeat the procedure with explanted calcified human aortic valve leaflets.

LONGITUDINAL IN-VIVO STUDY ON BISPHOSPHONATE TREATMENT IN DEVELOPMENT OF VASCULAR CALCIFICATION

Authors: Amirala Bakhshian Nik, Joshua D. Hutcheson

Abstract

Calcium mineralization occurs physiologically through bone formation and pathologically in cardiovascular calcification. Bisphosphonates are common osteoporotic therapeutics, which stabilize calcium phosphate mineral. They also prevent mineral growth and maturation in cardiovascular tissue by chelating phosphate ions that are required for calcification. However, administration of these therapeutics led to increased rates of cardiovascular incidents in patients with cardiovascular event history. In this study, we hypothesized that bisphosphonates exacerbate mineral formation if given once calcification has begun. We analyzed calcification growth over 25 weeks in Apolipoprotein E-deficient (Apoe-/-) mice on an atherogenic diet (42% fat). Vascular calcification has been previously observed after 10 weeks of atherogenic diet in these mice. Following 5, 10, or 15 weeks of the diet, the mice received biweekly subcutaneous injections of ibandronate sodium bisphosphonate (2 mg/kg). Tail-vein injections of calcium tracer dyes, namely Alizarin Red S, Calcein green, Calcein Blue, and near-infrared OsteoSense, were given after 10, 15, 20, and 25 weeks of the diet, respectively, to track the calcification at these time-points. Bisphosphonate treatment increased calcification in the aorta for groups treated after 10 and 15 weeks of the diet compared to the control group (biweekly saline injection) by 68 and 23 percent, respectively. We observed no change in the group treated after 5 weeks of the diet compared to the control group. In vivo data support our hypothesis that bisphosphonate promotes cardiovascular calcification if given after initial mineral nucleation. These studies could inform clinical decisions regarding potential cardiovascular effects of bisphosphonate treatment.

EXPERIMENTAL INTEGRATION OF A SPATIAL FREQUENCY DOMAIN SPECTROSCOPY AND PULSE CAM SYSTEM FOR QUANTIFYING CHANGES IN SKIN OPTICAL PROPERTIES AND VASCULATURE AMONG INDIVIDUALS WITH OBESITY

Authors: Andres J. Rodriguez, Tananant Boonya-ananta, Ashok Veeraraghavan, Jessica C. Ramella-Roman

Abstract

Obesity leads to a higher risk of diabetes and cardiovascular diseases. The use of wearables to manage and improve healthy lifestyle among the obese has sometimes lead to weight loss. Wearable devices can measure biomarkers; including heart rate, heart rate variability, perfusion, pressure pulse-wave velocities, among others. While electrical or thermal sensors used in older wearables resulted in operational challenges, newer optical sensors have emerged to be a more robust component to use. Current optical sensors rely on fluctuations due to spatio-temporal variations in absorption of tissue. Individuals having a high Body Mass Index (BMI) with a thicker layer of adipose tissue scatter the signal, yielding poorer optical contrast and signal to noise ratio. Moreover, higher BMI alters chemical concentrations– like water, oxygenation, and blood volume in the dermal layer– and thus the optical properties (OP). Although OP of the skin exist in literature, no study has strictly recorded the effect and magnitude of a higher BMI on them. An optical system combining Spatial Frequency Domain Spectroscopy (SFDS) with Video Imaging (PulseCam) could be helpful in characterizing OP of the obese. SFDS separates and quantifies the absorption coefficient and reduced scattering coefficient. PulseCam tracks changes in vascularization through high-resolution blood perfusion maps. We will create tissue-mimicking phantoms for proper calibration and verification of our integrated system. This study will allow us to better understand and characterize how the anatomical and physiological changes in the obese skin affects the use optical sensors to record physiological biomarkers.

THE ROLE OF DYNAMIC MECHANICAL ENVIRONMENTS IN VESICLE TRAFFICKING

Authors: Daniel A. Cambron, Mohammad Shaver, Joshua D. Hutcheson

Abstract

Extracellular vesicles (EVs) mediate interactions between cells and with the extracellular matrix. The aim of this study is to elucidate how vesicle trafficking is affected by changes in the mechanical environment of the cell. Caveolin-1 (cav-1), a structural protein located in caveolae invaginations of the cell membrane, is required for the formation of a specific subset of EVs that participate in pathological remodeling in coronary artery disease. Caveolae are known to participate in mechanotransduction, and given that vascular smooth muscle cells (SMCs) reside within dynamic vascular tissues, studies into the mechanical-dependent regulation of cav-1 positive EV formation could provide new insight into the role of mechanics in arterial remodeling. We inhibited known mechanotransductive proteins to assess changes in the formation and release of cav-1 positive EVs from SMCs exposed to cyclic stretch or no stretch for 72 hours. The greatest amount of cav-1 internalization and cav-1 positive EV release occurred under the cyclic stretch condition when compared to the no stretch condition. We then treated SMCs with ROCK inhibitor (ROCKi) or Src inhibitor (Srci) and evaluated cytoskeletal rearrangement and cav-1 levels after 72 hours. SMCs treated with ROCKi showed increased cav-1 positive EV release under both cyclic stretch and no stretch conditions. On the other hand, Srci treatment caused the SMCs to exhibit decreased levels of cav-1 positive EV release when compared to ROCK inhibition and control.

TORPEDO-SHAPED BIOREACTOR DESIGN FOR TUBULAR HEART-VALVE BIOSCAFFOLD

Authors: Manuel Perez-Nevarez, Brittany Gonzalez, Asad Mirza, Marcos Gonzalez, Sharan Ramaswamy

Abstract

Tissue engineered heart valve (TEHV) constructs have been studied as replacement for diseased or disfunctional heart valves. Porcine small intestinal submucosa (PSIS) decellularized tissue has been previously evaluated as implant material to replicate heart valve function. Ideally, TEHV are intended to integrate into the native somatic tissue. To achieve this, we have previously seeded PSIS with Bone Marrow Stem Cells (BMSC) with the aim of achieving de novo extracellular matrix production and integration into native tissue. Our previous tissue engineering bioreactor studies have shown that flow induced shear stress can influence vascular phenotype development and tissue formation. Flow-conditioning bioreactors have been designed to replicate physiologically relevant shear stresses and oscillatory shear forces experienced by native vascular tissue. We have developed a 2nd generation bioreactor system that can include provisions for the mechanical conditioning of tubular-shaped PSIS scaffolds. The system includes a torpedo-shaped sample holder that was designed to accommodate two cylindrically-shaped tubular scaffolds while retaining the ability to produce physiologically relevant hemodynamic shear forces over the scaffold surfaces. The dimensions of the bioreactor chamber were selected to maintain relevant oscillatory shear stress forces over the scaffold surfaces. This serves to subject the tubular PSIS specimens to sinusoidal flow and pressure variations produced by heart pulsation during its heartbeat. Our overall objective is the design a bioreactor system that can generate implantable tissues by conditioning BMSC seeded PSIS scaffolds to promote tissue formation and subsequently produce TEHV constructs that can be then implanted in vivo.

OSCILLATORY SHEAR STRESS EFFECTS ON MESENCHYMAL STEM CELLS IN MONOLAYER CULTURE

Authors: Elizabeth Cheng, Denise Hsu, Alexandra Tchir, Sharan Ramaswamy

Abstract

Heart valve disease, often treated by the replacement of the affected heart valve with a prosthetic heart valve, has increasingly become a problem requiring alternative methods of treatment for those who cannot sustain a prosthetic heart valve. Tissue engineered heart valves (TEHVs) present to be a viable method to be further explored, as TEHVs have the ability to develop and grow. Human bone marrow stem cells (HBMSCs) have the ability to differentiate, gaining characteristics and functions of a different cell. Oscillatory shear stress has proved to be a factor in aiding the development of heart valve cells. The objective of this study is to determine the most suitable environmental conditions for valve tissue growth using HBMSCs. Previous computational research conducted on determining the most effective range of oscillatory shear index (OSI) necessary for favorable gene expression garnered a range of 0.18 to 0.23 OSI. Therefore, the flow condition of 0.25 OSI on the HBMSCs is expected to elicit the most promising phenotype. HBMSCs were cultured and plated into separate wells for introduction into the BioFlux system. The BioFlux system was utilized to induce oscillatory shear stress patterns of zero, 0.25, and 0.5 OSI for 48 hours each. RNA from the HBMSCs was then extracted in order to analyze the cell's gene expression of specific heart valve genes using quantitative polymerase chain reaction (qPCR).

DECELLULARIZATION WITH THE ENHANCED RETENTION OF BIOSCAFFOLD MATRIX COMPONENTS FOR HEART VALVE REGENERATIVE APPLICATIONS

Authors: Ariadna Herrera, Brittany Gonzalez, Carl Granath, Cecilia Österholm Corbascio, Sharan Ramaswamy

Abstract

Congenital heart problems are the most common type of birth abnormality, affecting 8 out of 1000 live births in the U.S. (www.aha.org). Clinical solutions for critical valve defects in pediatrics are severely limited by the unavailability of small prosthetic valves; moreover, artificial valves cannot adapt to somatic growth. Therefore, tissue engineered heart valves are of interest as they can provide for growth, self-repair, infection resistance, and can be a permanent approach for replacing defective heart valves. We investigated porcine small intestinal submucosa (CorMatrix, Roswell, GA) longitudinally as a viable bioscaffold in an animal model. An explant of the PSIS mitral valve (11 months' post-implantation) exhibited a chronic immune response, which we speculate is due to the reminiscence of porcine cells. Thus, we hypothesize that the application of a more cautious, yet thorough decellularization technique will further remove porcine cells (acellular) while maintaining the integrity of the extracellular matrix (ECM), due to the added care involved in minimizing hostile detergent exposure to the ECM. Specifically, the decellularized PSIS scaffolds will be treated with a non-ionizing detergent for 12 and 24 hours to find the optimal processing time. After detergent removal the extent of cell removal will be assessed by DAPI staining of the nucleus and matrix integrity retention will be analyzed through histological staining specifically for collagen, GAGs and elastin, the main ECM components of the valve. The re-decellularized scaffolds will be compared to the original scaffolds to see how effective our gentle decellularization technique was at removing the cells while minimizing damage to the ECM. This acellular PSIS scaffold with intact ECM components is ideal for implantation because it will mitigate or completely remove the immune response that occurs, allowing for proper de novo growth. Moreover, the retention of additional ECM components in the bioscaffold will help to further promote de novo valvular tissue formation via chemotaxis.

VIMENTIN, CAV-1, AND VESSEL MECHANICS: IMPLICATION ON CARDIOVASCULAR DISEASE PROGRESSION

Authors: Emma Drabbe, Nicole van Engeland, Mohamad Shaver, Joshua D. Hutcheson, Carlijn Bouten

Abstract

Cardiovascular diseases (CVDs) are a major cause of morbidity and mortality worldwide. Pathological pathways leading to CVDs have been linked to factors such as vessel wall mechanics, intracellular vimentin integrity, and caveolin-1 positive extracellular vesicle release. The intermediate filament vimentin functions as an important protein in the vascular wall. It is involved in maintaining mechanical properties, cell adhesion and several signaling pathways in vascular cells. A co-culture of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) in a microfluidic vessel-wall-on-a-chip device was created to study the role of vimentin in a physiologically relevant hemodynamic environment encompassing both fluid shear stress and cyclic strain. Furthermore, a lentiviral-mediated vimentin knockdown in ECs and VSMCs is created to study the impact of vimentin depletion on vascular cell function. The results show that mechanosensitive vimentin plays an important role in maintaining an in-vivo cell phenotype in both ECs and VSMCs. Jiu et al. report that vimentin restricts intracellular caveolin-1 distribution. Understanding the interaction between vimentin and caveolin-1 is important to target CVDs. Furthermore, Bartolák-Suki et al. comment on the importance of variable strain patterns when recapitulating physiologically relevant vessel models in-vitro. Therefore, the interaction of caveolin-1 and mechanosensitive vimentin in VSMCs is studied when exposed to variable and monotonous cyclic strain using a Flexcell® system. Elucidating the role of different cyclic strain patterns will help to build more physiologically relevant in-vitro models, such as a microfluidic vessel-wall-on-a-chip device.

MASS SPECTROMETRY ANALYSES OF STEM CELL-DERIVED EXOSOMES FOR CARDIAC REGENERATION

Authors: Reem Ekhraiwesh, Yih-mei Lin, Sharan Ramaswamy

Abstract

Exosomes are nanosized extracellular vesicles in eukaryotic cells that carry and transfer proteins. Current efforts have shown that stem cell-derived exosomes act as a communicator between cells by delivering specific substances. These substances including certain proteins have beneficial effects on cardiac regeneration. We hypothesize that physiologically-relevant oscillatory-flow conditioned stem cells will secrete exosomes containing augmented levels of protein-cargo of critical importance to cardiac restore and revitalize processes due to the enhanced protein translation that will occur via cell mechanosensitive pathways. A preliminary experiment was done by using bone marrow mesenchymal stem cells (MSCs) that were seeded onto porcine small intestinal submucosa (PSIS) bio-scaffolds and were cultured for 8 days in a rotisserie. Several cardiovascular relevant proteins such as fibronectin, titin, integrin alpha-9, complement 3, periostin, and epiplakin were found in the previous experiment. Our current works will aim to have a further understanding of which conditioned group would have a relatively higher appearance of cardiovascular relevant proteins in the mass spectrometry (MS) analysis. The groups that will be testing in rotisserie include MSCs, MSCs incorporated with EV Boost, co-culture of MSCs and CD34+ stem cells, and co-culture of MSCs and CD34+ stem cells incorporated with EV Boost. We will perform exosome isolation and proceed to proteomic analysis by using MS technique. For the future work, we will continue the analysis of MS and move forward to investigate exosomes by using a bioreactor which will potentially accelerate the production of cardiovascular relevant proteins with higher quality under the mechanical flow condition.

THE USE OF OPTIMIZED STEM CELL-DERIVED EXOSOMES IN FACILITATING CARDIOVASCULAR REGENERATION

Authors: Yih-Mei Lin, Manuel Perez, Brittany Gonzalez, Reem Ekhraiwesh, Sharan Ramaswamy

Abstract

Over the years, cardiovascular diseases (CVD) have become the major cause of mortality. Unfortunately, the heart has limited capability to regenerate from disease-inducing damage, which ultimately leads to heart failure. Previous studies have shown that adult mesenchymal stem cells (MSCs) have the ability to differentiate into different cell types. However, MSCs have a low survival rate and suffer from suboptimal engraftment. An alternative approach in cardiovascular regeneration may be via the delivery of the secretory factors released from MSCs. Exosomes are secreted by various cell types and serve as a cargo of molecular factors which make delivery to a site of tissue damage and/or injury. To investigate the methods to enhance secretion of exosomes, our study involved a bioreactor device to create a mechanical flow environment to stimulate stem cells. Moreover, we increased the MSC seeding density (~ 35 x 106 cells) and incorporated a commercially-available exosome-augmenter (EV Boost™ ™, RoosterBio, Frederick, MD) for additional elevated and rapid exosome production. Finally, CD 34+ hematopoietic stem cells (HSCs) (~ 0.5 x 106 cells) were co-cultured with MSCs to explore the effect of HSCs on further increasing the quantity and quality of exosomal production. In this study, mass spectrometry, cytokines panel, and gene expression analysis techniques will be used to characterize the cardioprotective factors released from the exosomes. It is expected that these approaches will lead to an optimized bio-manufacturing protocol for producing stem cell-derived e xosomes for more effective treatment of CVD than is currently available, via the induction of cardiovascular regeneration.

A STITCH IN TIME: CHANGING PRESENTATIONS OF AORTO-RIGHT VENTRICULAR FISTULA COMPLICATING AORTIC VALVE REPLACEMENT

Authors: Elan Baskir, Mario Zevallos, Steven Borzak

Abstract

Purpose: An aorto-right ventricular fistula is an uncommon finding in patients after surgical aortic valve replacement (SAVR). It can present as a new continuous murmur, and first sign of prosthetic valve infective endocarditis. How the mechanism and approach of this rare complication differs from transcatheter aortic valve replacement (TAVR) is debated. Methods: We conducted a comprehensive literature review of aorto-cavitary fistulae after SAVR and TAVR. Then, we conducted a convenience case review of two patients in our clinic with aorto-right ventricular fistulae, complications from a SAVR and TAVR, respectively. Notes and imaging from clinic visits and hospital charts were analyzed. Results: Case 1: A 78-year-old male with a history of symptomatic mixed aortic valve disease and atrial fibrillation underwent SAVR and ascending aortic aneurysm repair. At 18 months post-SAVR, a new continuous murmur was heard at the left sternal border. A transthoracic echocardiogram revealed a dilated aortic root, and an aorto-right ventricular fistula. 4 months later, the patient developed fever and Strep viridans bacteremia with a negative transesophageal echocardiogram for vegetations. He underwent homograft aortic root replacement and recovered uneventfully. Case 2: An 82-year-old male with a history of minimally symptomatic critical aortic stenosis, persistent atrial fibrillation, coronary artery disease, hypertension, and hyperlipidemia underwent TAVR. At 4 weeks post-TAVR, he was readmitted for edema, heart failure, and failure to thrive. Although no continuous murmur was heard, an earlier echocardiogram showed an aorto-right ventricular fistula, confirmed by transesophageal echocardiogram and right heart catheterization. The fistula was closed percutaneously and he recovered uneventfully. Conclusions: Aorto-RV fistulae may be more common in TAVR than SAVR populations, less likely infectious, and have a less typical clinical presentation, with a poorly audible continuous murmur. With the decreasing incidence of peri-prosthetic aortic insufficiency, aorto-cavitary fistula should be considered as a cause of failure to thrive after TAVR.

MODELING OF A PHOTOPLETHYSMOGRAPHIC (PPG) WAVEFORM THROUGH MONTE CARLO AS A METHOD OF DERIVING BLOOD PRESSURE IN INDIVIDUALS WITH OBESITY

Authors: Tananant Boonya-ananta, Andres J. Rodriguez, Anders K. Hansen, Joshua D. Hutcheson, Jessica C. Ramella-Roman

Abstract

Blood pressure can be used as an indicator of an individual's risk for cardiovascular disease. The common practice of blood pressure measurement using a cuff-based system provides a snapshot of blood pressure at a single instance in time and can be inconvenient and intrusive. Blood pressure measuring devices are known to have variation and inaccuracies when applied to larger arm sizes as seen in individuals with obesity. The development of optical methods to determine blood pressure could provide continuous monitoring of blood pressure through techniques such as pulse transit time or pulse arrival time when used with echocardiogram. These techniques are based on optical techniques such as photoplethysmography (PPG), but little is known of the optical transport in the skin of the obese. We propose that accurate waveform replication is required for the derivation of blood pressure applied to individuals with obesity. Here we use the Monte Carlo framework to develop the PPG waveform as a means to derive blood pressure through cuff less techniques. The development of a simulated waveform incorporates realistic changes in the artery related to its biomechanical properties as a pressure wave is propagated through the vessel. It is shown that a change in vessel pressure and geometry directly affects captured optical signal. The system can account for variations in body-mass index to compensate for geometrical changes in adipose tissue layer and changes in optical properties.

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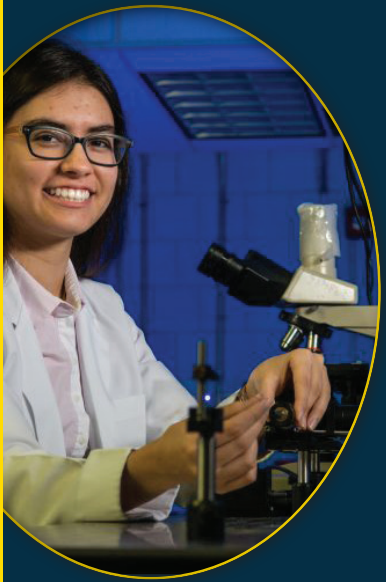

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