MAZANKOWSKI
CARDIAC SCIENCES
RESEARCH DAY

UNIVERSITY OF ALBERTA
JUNE 12, 2015
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CARDIAC SCIENCES RESEARCH DAY

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June 12, 2015

Dear Colleagues,

Welcome to the 19th annual Cardiac Sciences Research Day. It is always a pleasure and a honour to preside over this day of showcasing of the best cardiovascular science developed in our institution. Both the basic and clinical sciences are well represented and numerous interesting abstracts have been submitted. This is living proof of the productivity and vitality of our cardiovascular environment.

We are joined in our celebrations by two brilliant speakers and investigators.

• Dr. Peter Ganz, MD, Chief, Division of Cardiology and Director, Centre of Excellence in Vascular Research San Francisco General Hospital. Maurice Eliaser Distinguished Professor of Medicine, University of California, San Francisco, CA. Dr. Ganz will be presenting: *Proteomics of Cardiovascular Disease.*

• Dr. Zahl A. Fayad, PhD, Director of the Translational and Molecular Imaging Institute and Professor of Radiology and Medicine (Cardiology) Mount Sinai Hospital New York, NY. Dr. Fayad will be presenting: *Imaging and Nanomedicine in Inflammatory Atherosclerosis.*

I would like to extend my thanks to all the colleagues who helped in the organization of this day (committee members, judges, chairs, administrative assistants) and to the industry sponsors who gave generously to support this day. Without their support this important initiative would be very difficult to stage.

I hope you will enjoy this day of science and that you will join us in the poster area and conference room throughout the day and at the end of the day for a light reception in the atrium.

Warm regards,
Paolo Raggi, MD, FACC, FACP, FASNC
Chair, CSRD Organizing Committee
19TH ANNUAL MAZANKOWSKI CARDIAC SCIENCES RESEARCH DAY
0745 – 1730 | FRIDAY, JUNE 12, 2015
ALLARD FAMILY LECTURE THEATRE, ROOM 1080
KATZ GROUP CENTRE FOR PHARMACY AND HEALTH RESEARCH

0645 - 0745  Registration & Poster Set-up
Location: Katz Group Centre Foyer

0745 - 0800  Introduction to Grand Rounds
Dr. Ross Tsuyuki

Welcome and Introductions – Dr. Paolo Raggi
Chair, Cardiac Sciences Research Day Committee

0800 - 0900  Internal Medicine Grand Rounds Speaker
Peter Ganz, MD
Chief, Division of Cardiology
Director, Center of Excellence in Vascular Research
San Francisco General Hospital
Maurice Eliaser Distinguished Professor of Medicine
University of California, San Francisco, CA

Topic: Proteomics of Cardiovascular Disease

0900 - 1000  Coffee Break / Poster Viewing

1000 - 1130  Podium Abstract Session
Chairs – Dr. Wayne Tymchak & Dr. Richard Lehner

1000  Janek Senaratne, Colleen Norris, Michele Graham, Jayan Nagendran, Darren Freed, Jonathan Afilalo, Sean Van Diepen

Routine Coronary Artery Bypass of Angiographically Borderline Coronary Artery Stenosis is not Associated with Improved Survival

1015  Anne Lee Solevag, Georg Schmolzer, Megan O’Reilly, Min Lu, Tze-Fun Lee, Lisa Hornberger, Po-Yin Cheung

Continuous Chest Compressions and Asynchronous Ventilation with 21% or 100% Oxygen in Severely Asphyxiated Piglets with Cardiac Arrest

1030  Chye Teik Ooi, Jacqueline Krysa, Hussein Abujrad, Janice Mayne, Kathy Henry, Marion Cousins, Angela Raymond, Colette Favreau, Monica Taljaard, Michel Chrétien, Majambu Mbikay, Spencer Proctor, Donna Vine

The Effect of PCSK9 Loss of Function Variants on Postprandial Lipid and APOB-Lipoprotein Response
1045 Jody Groenendyk, Dukgyu Lee, Joanna Jung, Gary L. Lopaschuk, Luis B. Agellon, Marek Michalak
*Increased Expression of Calreticulin in the Heart: Cardiac Fibrosis and Heart Failure*

1100 Sumandeep Dhesi, Anamaria Savu, Padma Kaul, Justin A. Ezekowitz
*Impact of Diabetes During Pregnancy and the Risk of Peripartum Cardiomyopathy: A Population-Level Analysis of 213,058 Women*

1115 Maria Akhonkh, Victor Samokhvalov, Feng Hua Yang, Xiuhua Wang, Ratnaeep Basu, Gavin Y. Oudit, Zamaneh Kassiri, Woo Jung Cho, Bruce Hammock, John Seubert
*Inhibition of Soluble Epoxide Hydrolase Limits Mitochondrial, Damage and Preserves Functioning Ischemic Injury*

1130 - 1250 **Lunch / Poster Viewing**

1255 - 1300 **Introduction of Dr. Joseph Dvorkin**
Memorial Lecture Speaker – Dr. Paolo Raggi

1300 - 1400 **Speaker – Zahi A. Fayad, PhD**
Director of the Translational and Molecular Imaging Institute and Professor of Radiology and Medicine (Cardiology)
Mount Sinai Hospital, New York, NY
*Topic: Imaging and Nanomedicine in Inflammatory Atherosclerosis*

1415 - 1515 **Podium Abstract Session**
Chairs – Dr. Justin Ezekowitz & Dr. Spencer Proctor

1415 Sunjidadul Islam, Yutaka Yasui, Padma Kaul, Ariane J. Marelli, Andrew S. Mackie
*Congenital Heart Disease Hospitalizations in Canada: A 10-Year Experience*

1430 Bruce Motyka, Katrina Labonte, Fahim H. Rahman, Jean Pearcey, Kesheng Tao, Michael Mengel, Banu Sis, Peter J. Cowan, Lori J. West
*Investigation of A-Antigen Specific Tolerance Following ABO-Incompatible Heart Transplantation (ABOI HTX) Using A Novel Blood Group A Transgenic Mouse Model*
1445  Shine Kumar, Mohammed Elgendi, Long Guo, Prashant Bobhate, Ian Adatia
*N-Terminal Pro Brain Natriuretic Peptide Levels in Children with Pulmonary Artery Hypertension*

1500  Vaibhav B. Patel, Jun Mori, Brent A. McLean, Nirmal Parajuli, Ratnadeep Basu, Subhash K. Das, Thamarajan Ramprasad, Josef M. Penninger, Maria B. Grant, Gary D. Lopaschuk, Gavin Y. Oudit
*Angiotensin Converting Enzyme 2 Deficiency Results in Epicardial Adipose Tissue Inflammation, Cardiac Insulin Resistance and Heart Failure with Preserved Ejection Fraction in Response to Diet-Induced Obesity*

1515 - 1530  Coffee Break / Poster Viewing

1530 - 1630  Podium Abstract Session

*Chairs – Dr. Nadia Jahroudi & Dr. Bibiana Cujec*

1530  Vikram Gurtu, Adam Kinnaird, Linda Webster, Evangelos Michelakis
*Scleroderma Associated Pulmonary Arterial Hypertension is Associated with a High Prevalence of Aortic Stenosis*

1545  Nikole J. Byrne, Jody Levasseur, Miranda M. Sung, Grant Masson, Jamie Boisvenue, Martha E. Young, Jason Dyck
*Normalization of Cardiac Energy Metabolism Precedes Regression of Left Ventricular Hypertrophy and Improved Function in Mice with Heart Failure*

1600  Jay Shavadia, Robert Welsh, Anthony H. Gershlick, Yinggan Zheng, Kurt Huber, Sigrun Halvorsen, Phillippe Gabriel Steg, Frans Van de Werf, Paul W. Armstrong
*Relationship Between Arterial Access and Outcomes in a Pharmacoinvasive Versus Primary PCI Strategy in ST-Elevation Myocardial Infarction: Insights from the Strategic Reperfusion Early After Myocardial Infarction (STREAM) Study*

1615  Westam Bahitham, Jihong Lian, Lena Li, Randal Nelson, Aducio Thiesen, Richard Lehner
*Genetic Variation in Human Carboxylesterase 1 (CES1) Confers Protection Against Nonalcoholic Fatty Liver Disease*

1630 - 1700  Abstract Judging, Awards Ceremony & Closing Remarks

1700  Reception
GUEST SPEAKER BIOGRAPHIES
PETER GANZ, MD

Dr. Ganz is the Chief of Cardiology and the Director of the Center of Excellence in Vascular Research at the San Francisco General Hospital and the Maurice Eliaser Distinguished Professor of Medicine at the University of California, San Francisco. Dr. Ganz has been a pioneer and a leader in translational and clinical cardiovascular research. His interests have focused on understanding key elements of human atherosclerosis including vascular endothelial function, the biology of nitric oxide, systemic and vascular inflammation and atherosclerotic plaque instability. Most recently, Dr. Ganz is making discoveries in the proteomics of cardiovascular diseases and the biology of aging. Dr. Ganz has authored over 200 peer reviewed articles, many published in the most prestigious journals. He has served on steering committees of numerous clinical trials. Many fellows who worked in Dr. Ganz’s laboratory have gone onto key leadership positions in academic medicine nationally and internationally. Dr. Ganz received his M.D. from Harvard Medical School, completed his residency at the Massachusetts General Hospital and cardiovascular fellowship at the Brigham and Women’s Hospital. He spent 25 years directing research in the Cardiac Catheterization Laboratories at the Brigham and Women’s Hospital and Harvard Medical School, prior to arriving to the University of California, San Francisco in 2008.
ZAHI A. FAYAD, PHD

Dr. Fayad serves as professor of Radiology and Medicine (Cardiology) at the Mount Sinai School of Medicine. He is the Director of the Translational and Molecular Imaging Institute; Vice chair for Research, Department of Radiology at the Icahn School of Medicine at Mount Sinai. Dr. Fayad’s interdisciplinary and discipline bridging research - from engineering to biology and from pre-clinical to clinical investigations - has been dedicated to the detection and prevention of cardiovascular disease with many seminal contributions in the field of multimodality biomedical imaging (MR, CT, PET and PET/MR) and nanomedicine. He has authored more than 300 peer-reviewed publications (h-index of 67 as of 01/31/2015), 50 book chapters, and over 400 meeting presentations. He is currently the Principal Investigator of multiple grants from the National Institutes of Health’s National Heart, Lung and Blood Institute and National institute of Biomedical Imaging and Bioengineering with a recent large award from NHLBI to support the Program of Excellence in Nanotechnology. In addition, he serves as Principal Investigator of the Imaging Core of the Mount Sinai National Institute of Health (NIH)/Clinical and Translational Science Awards (CTSA). He is Associate Editor for the Journal of the American College of Cardiology-Imaging (JACC Imaging), Section Editor for Journal of the American College of Cardiology (JACC) and Consulting Editor for Arteriosclerosis Thrombosis and Vascular Biology (ATVB) and past associate Editor of Magnetic Resonance in Medicine (MRM).
GUEST SPEAKER ABSTRACT
Atherosclerosis is a chronic progressive disease, affecting the medium and large arteries, in which lipid-triggered inflammation plays a pivotal role. The major clinical manifestations of atherosclerosis are coronary artery disease (CAD), leading to acute myocardial infarction (MI) and sudden cardiac death; cerebrovascular disease, leading to stroke; and peripheral arterial disease, leading to ischemic limbs and viscera. These complications of atherosclerosis are leading causes of death worldwide. Despite progress in medical and revascularization therapies for atherothrombotic disease, the incidence of MI and stroke remain high under the current standard of care, and the past decade has generated few new medical therapies to prevent atherosclerosis-induced events. Similarly, current diagnostic approaches to atherosclerosis do not accurately identify those individuals who will suffer an ischemic complication. The field of atherosclerosis is therefore ripe for reengineering in both the therapeutic and diagnostic arenas. Research into the process of atheroma lesion development and maturation has implicated many immune cells including lymphocytes, dendritic cells, and neutrophils. The most numerous cells in atherosclerotic plaque are macrophages, which are leukocytes that are central to the innate immunity. Because they play a major role in instigating plaque development and complication—both of which are inflammation-related disease processes—leukocytes are promising targets for more effective atherosclerosis treatments. However, the complexity of the immune system and its role as a defensive force against infection require novel tools to very precisely identify and treat the inflammatory cells that promote atherosclerosis. Biomedical engineering offers unique possibilities for diagnosing and treating atherosclerotic plaque inflammation. Thus, interfacing engineering with immunology will be essential to meaningful advances in disease management.

This talk will discuss how recent discoveries in atherosclerosis immunology can provide opportunities for diagnostic imaging of atherosclerotic plaques and cardiovascular complications of atherosclerosis, including translatable molecular imaging techniques. Integrated diagnostic modalities have uncovered new pathways that can serve as potential diagnostic and therapeutic targets, and show that these pathways can be specifically modulated by nanomedicine based interventions.

Objectives:

1) Define Nanomedicine and its opportunity in cardiovascular disease detection and treatment
2) Demonstrate the methods of plaque molecular imaging with MR Imaging, PET, CT.
3) Discuss the advantages and limitations of plaque molecular imaging using MR Imaging, PET, CT.
4) Discuss the preclinical and clinical relevance of plaque molecular imaging by MR Imaging, PET, CT.
5) Discuss novel methods for atherosclerotic plaque treatment using nanomedicine.
ORAL ABSTRACTS
ROUTINE CORONARY ARTERY BYPASS OF ANGIOGRAPHICALLY BORDERLINE CORONARY ARTERY STENOSES IS NOT ASSOCIATED WITH IMPROVED SURVIVAL

Janek Senaratne, Colleen Norris, Michele Graham, Jayan Nagendran, Darren Freed, Jonathan Afilalo, Sean Van Diepen

Background: Coronary artery bypass grafting (CABG) improves outcomes in patients with multi-vessel coronary artery disease. Bypass of angiographically significant lesions ≥70% is recommended yet there is little evidence to guide decision making for angiographically borderline 50-69% lesions (ABL), which has led to wide variability in practice patterns.

Methods: Between 2007 and 2013, 3,195 patients in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry underwent isolated first CABG with at least 2 distal anastomoses. Patients with an isolated ABL (50-69%) of the proximal segment of a major epicardial coronary vessel (excluding the left main) on the pre-operative angiogram were included in the study. The primary outcome of interest was long-term mortality.

Results: Among the 350 patients with an ABL, 268 (76.6%) were surgically bypassed. Mean follow-up was 4.2 ± 1.7 years. Patients with a bypassed ABL tended to be older (62.5 vs 66.1 years, p=0.01) but were otherwise similar in terms of sex, comorbidities, diabetes, ejection fraction, and number of coronary stenoses. Cardiopulmonary bypass time was longer in patients with bypassed ABL (104.2 vs 90.4 minutes, p<0.001). Compared to non-bypassed ABL, bypassed ABL was associated with a trend towards increased long term mortality (adjusted odds ratio 2.96: 95% confidence interval, 0.90 – 9.68, p=0.07). Similarly no differences were observed in either 30-day (0.0% vs 1.1%, p=0.336) or 1-year mortality (0.0% vs 4.1%, p=0.062). No interactions between major epicardial ABL vessel location and mortality were identified. Repeat revascularization of ABL bypass grafts was numerically higher (0.0% vs 4.1%, p = 0.107).

Conclusion: In a large unselected cohort of patients with ABL, bypass of these 50-69% lesions is frequently performed and not associated with improved long-term survival. Our findings suggest that the routine surgical revascularization of ABLs may not be warranted.
CONTINUOUS CHEST COMPRESSIONS AND ASYNCHRONOUS VENTILATION WITH 21% OR 100% OXYGEN IN SEVERELY ASPHYXIATED PIGLETS WITH CARDIAC ARREST

Anne Lee Solevåg, Georg Schmölzer, Megan O’Reilly, Min Lu, Tze-Fun Lee, Lisa Hornberger, Po-Yin Cheung

Background: While exposure to 100% oxygen may be harmful, there is insufficient data on the effectiveness of 21% oxygen in cardiac arrest and prolonged resuscitation in asphyxiated neonates. An advantage of performing uninterrupted chest compressions (CC) in adults has been demonstrated. The balancing concerns of reoxygenation and providing organ perfusion make cardiopulmonary resuscitation (CPR) of asphyxiated infants different from adult CPR. In a piglet model of severe asphyxia and cardiac arrest, we hypothesized that combining continuous CC and asynchronous ventilation (CCaV) with 21% oxygen would improve CPR outcomes vs. the currently recommended CC:ventilation ratio of 3:1 (3:1 C:V CPR) with 100% oxygen.

Methods: Thirty-two piglets (1-3d old) were instrumented and asphyxiated until cardiac arrest. Piglets were randomized to receiving 3:1 C:V CPR or CCaV using 21% or 100% oxygen (four groups, n=8 each). CPR characteristics, time to return of spontaneous circulation (ROSC), and mortality were compared among groups. Results were also stratified according to 21% vs. 100% oxygen, and 3:1 C:V CPR vs. CCaV.

Results: At cardiac arrest, median (IQR) arterial pH was 6.6 (6.5-6.9), paCO2 78 (48-97)mmHg and lactate 18 (15-19)mmol/L. CPR parameters and outcome data are presented in Table 1. Time to ROSC and mortality were similar when all four groups were compared. There was no difference in CPR parameters, time to ROSC or mortality between oxygen groups. However, CPR with 21% oxygen resulted in a higher left ventricular stroke volume compared to 100% oxygen at 30min (p=0.01) and 4h (p=0.06) after ROSC. CCaV resulted in lower tidal volumes (p=0.013), more CC/min (p=0.042), but similar diastolic blood pressure (DBP) compared to 3:1 C:V CPR (p=0.35).

Table 1: CPR parameters and survival 4h after ROSC

<table>
<thead>
<tr>
<th></th>
<th>3:1 C:V 21%</th>
<th>3:1 C:V 100%</th>
<th>CCaV 21%</th>
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</tr>
</thead>
<tbody>
<tr>
<td>VT (mL/kg)</td>
<td>17 (11-22)</td>
<td>21 (15-22)</td>
<td>13 (10-16)</td>
<td>14 (13-15)</td>
</tr>
<tr>
<td>MV (mL/kg/min)</td>
<td>390 (373-528)</td>
<td>578 (420-691)</td>
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<td>CC/min (n)</td>
<td>92 (83-94)</td>
<td>85 (77-90)</td>
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<tr>
<td>Achieving ROSC (n (%))</td>
<td>6 (75)</td>
<td>6 (75)</td>
<td>8 (100)</td>
<td>5 (63)</td>
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<tr>
<td>Time to ROSC (sec)</td>
<td>120 (110-726)</td>
<td>175 (91-823)</td>
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<td>Survival to 4 h after ROSC</td>
<td>2 (25)</td>
<td>4 (50)</td>
<td>3 (38)</td>
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Data are presented as median (IQR); VT – tidal volume, MV – minute ventilation, CCaV – continuous chest compressions and asynchronous ventilation.
Background: While exposure to 100% oxygen may be harmful, there is insufficient data on the effectiveness of 21% oxygen in cardiac arrest and prolonged resuscitation in asphyxiated neonates. An advantage of performing uninterrupted chest compressions (CC) in adults has been demonstrated. The balancing concerns of reoxygenation and providing organ perfusion make cardiopulmonary resuscitation (CPR) of asphyxiated infants different from adult CPR. In a piglet model of severe asphyxia and cardiac arrest, we hypothesized that combining continuous CC and asynchronous ventilation (CCaV) with 21% oxygen would improve CPR outcomes vs. the currently recommended CC:ventilation ratio of 3:1 (3:1 C:V CPR) with 100% oxygen.

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Data are presented as median (IQR); VT – tidal volume, MV – minute ventilation,

Conclusion: Despite a higher number of CC/min in CCaV piglets, DBP as an indirect measure of coronary perfusion pressure during CPR did not increase, and CCaV did not improve ROSC. Severe acidosis and possibly systemic vasodilation in profound asphyxia may contribute to a blunted effect of CCaV. The mechanism behind the difference in left ventricular stroke volume between oxygen groups will be explored in biochemical analyses of myocardial tissue. As 21% oxygen resulted in favorable hemodynamics after ROSC compared to 100% oxygen, 3:1 C:V CPR with 21% oxygen may be a reasonable approach.
THE EFFECT OF PCSK9 LOSS OF FUNCTION VARIANTS ON POSTPRANDIAL LIPID AND APOB-LIPOPROTEIN RESPONSE

Chye Teik Ooi, Jacqueline Krysa, Hussein Abujrad, Janice Mayne, Kathy Henry, Marion Cousins, Angela Raymond, Colette Favreau, Monica Taljaard, Michel Chrétien, Majambu Mbikay, Spencer Proctor, Donna Vine

Background: PCSK9 (proprotein convertase subtilisin/kexin type 9) is a protein that promotes low-density lipoprotein receptor (LDL-R) degradation resulting in increased plasma LDL-cholesterol (LDL-C), which is recognized as a major risk factor for cardiovascular disease (CVD). Loss-of-function (LOF) variants in the PCSK9 gene are associated with decreased LDL-R degradation, decreased serum LDL-C, and reduced CVD risk. In the postprandial state, the concentration of intestinal and hepatic lipoproteins (chylomicrons-CM and very low density lipoproteins -VLDL, respectively), and their remnants increase, while the concentration of LDL-C remains constant. Recent findings from the ‘Copenhagen Heart Study’ have identified elevated remnant-cholesterol apo-(apolipoprotein) B lipoproteins, which include VLDL and CM-remnants, as a causal risk factor for CVD. Remnants, like LDL, are cleared from the plasma by the LDL-R. In this study we hypothesized that LOF variants in the PCSK9 gene would result in increased clearance of apoB-remnant lipoproteins, and a decrease in fasting and the postprandial response of plasma triglycerides (TG) and apoB-remnant cholesterol lipoprotein concentrations.

Aim: To compare the fasting and postprandial response of TG and apoB-remnant cholesterol lipoproteins in subjects with and without PCSK9 LOF variants.

Methods: Subjects with > 1 LOF PCSK9 variant (n=22, R46L, A53V, and I474V) were compared with aged-matched controls (n=23). A high-fat meal was given and blood was drawn prior to (0hr), and at 2, 4, and 6 hrs following the meal. PCSK9 protein, LDL-C, TG, and Total apoB were quantified using colorimetric and ELISA methods. Total apoB is a measure of both hepatic (apoB-100) and intestinally derived CM (apoB-48) lipoproteins.

Results: Fasting plasma PCSK9 concentration did not differ between groups, however PCSK9 LOF variants showed a significant decrease in plasma PCSK9 concentrations in the postprandial phase compared to controls. Postprandial plasma TG (AUC and iAUC) was lower in the PCSK9 LOF variants compared to controls. As well, the postprandial plasma total apoB concentration for the variant group was decreased by 25% compared to the control group at 2 hr (100.1±5.63 vs. 124.1±5.87 mg/dL, p=0.03) and 4hr (100.5±9.06 vs. 121.66±7.67 mg/dL, p = 0.04), respectively. Furthermore, Total ApoB_AUC was significantly lower for the PCSK9 LOF variant group versus controls (p = 0.03).

Conclusion: These preliminary results demonstrate that the PCSK9 LOF variants have attenuated postprandial excursion in plasma TG and apoB-lipoproteins, which may contribute to reduced circulating apoB-remnant cholesterol lipoproteins and decreased CVD risk.
INCREASED EXPRESSION OF CALRETICULIN IN THE HEART: CARDIAC FIBROSIS AND HEART FAILURE

Jody Groenendyk, Dukgyu Lee, Joanna Jung, Gary L. Lopaschuk, Luis B. Agellon, Marek Michalak

Background: One detrimental aspect of cardiac failure is an increase in fibrosis with surplus deposition of extracellular matrix proteins which can reduce cardiac function with the underlying mechanism of why this happens still unclear. Increased abundance of calreticulin in adult heart has been associated with dilated cardiomyopathy and heart failure. Here, we discovered that increased expression of calreticulin in the adult mouse heart leads to severe cardiac fibrosis.

Methods: To investigate the mechanism behind calreticulin-dependent increase in cardiac fibrosis, we utilized microarray hybridization and monitored global gene expression in calreticulin transgenic hearts with impaired ER homeostasis. We performed biochemical and physiological experiments to monitor cardiac stress.

Results: We observed significantly enhanced expression of TGF-β1, a pleiotropic cytokine, as well as fibrillar collagens when compared with control hearts. Validation of protein expression showed that TGF-β1 expression and secretion into the circulatory system was significantly increased as well as receptor-regulated Smad2/3 expression, also activated in calreticulin transgenic hearts. Several pro-inflammatory factors and markers of fibrosis, including NFκB p65, and pro-inflammatory cytokines, TNFα, IL-1β, and IL-6, were noticeably up-regulated. The expression and localization of periostin, a ligand for integrins that supports cellular adhesion and migration, was increased in calreticulin transgenic hearts. ER stress was increased as measured by XBP1 splicing analysis (IRE1 activity), due to the overexpression of calreticulin in the heart. However, cardiac fibrosis triggered by calreticulin overexpression was effectively reduced by administration of tauroursodeoxycholic acid (TUDCA), possibly due to TUDCA’s inhibitory effects on ER stress.

Conclusion: We concluded that the mechanism leading to cardiac fibrosis in adult hearts overexpressing calreticulin may involve impaired ER homeostasis triggering activation of ER stress coping responses, activation the TGF-β1/Smad2/3 signaling pathway which may lead to cardiac fibrosis with this pathogenesis suppressed by TUDCA treatment.
IMPACT OF DIABETES DURING PREGNANCY AND THE RISK OF PERIPARTUM CARDIOMYOPATHY: A POPULATION-LEVEL ANALYSIS OF 213 058 WOMEN

Sumandeep Dhesi, Anamaria Savu, Padma Kaul, Justin Ezekowitcz

Background: Peripartum cardiomyopathy (PPCM) is a form of heart failure that occurs during or right after pregnancy. Maternal diabetes mellitus (DM) status is a risk factor for the development of PPCM. The objectives of our study were to: 1) determine the incidence of PPCM (overall, and across DM categories); and 2) examine obstetrical and neonatal outcomes associated with PPCM in a contemporary population level cohort in Alberta, Canada.

Methods and Results: The cohort consisted of 213 058 women who had a live birth between 04/2002 to 12/2009. Women with more than one pregnancy during the study time period were counted multiple times resulting in 294 443 birth events and 299 561 newborns. PPCM was defined based on the NHLBI/NIH definition, modified for registry and administrative data (ICD-10 codes O90.3, O99.4, I50, J81) occurring 2 months prior to delivery and up to 6 months postpartum. Women were categorized into three groups according to DM status: 1) no DM; 2) gestational diabetes mellitus (GDM); and 3) pre-existing DM (pre-DM).

A total of 769 cases of PPCM were identified resulting in an incidence rate for PPCM of 2.6/1000 (or 1/385) live births. The baseline characteristics of mothers with and without PPCM are presented in Table 1. Women with PPCM were more likely to be older, heavier, have multiple gestation, be induced, and undergo C-section. The incidence of PPCM was higher in pregnancies with pre-DM and GDM versus those without either (Figure 1). Neonatal mortality (within 28 days) was higher among infants born to mothers with PPCM and without DM or GDM (1.2%) compared to those with GDM only (0.2%, p<0.01), but not among those with pre-DM only (0.9%).

Conclusions: Both pre-existing DM and GDM were associated with an increased incidence of PPCM. Fetal outcomes were worse with maternal PPCM, and thus a multidisciplinary team of experts in obstetrics, maternal-fetal medicine, and cardiology should manage pregnancies complicated by PPCM.
Table 1. Selected baseline characteristics and outcomes among women with and without PPCM

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>No PPCM (N=293674)</th>
<th>PPCM (N=769)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean – yr + std</td>
<td>29.2 (5.5)</td>
<td>30.4 (6.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥ 35 yrs, n(%)</td>
<td>51824 (17.6)</td>
<td>200 (26.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre-pregnancy weight ≥ 91 kg, n(%)</td>
<td>25891 (8.8)</td>
<td>88 (11.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-singleton (multiple pregnancy)</td>
<td>5084 (1.7)</td>
<td>54 (7.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Primiparous</td>
<td>127256 (43.3)</td>
<td>379 (49.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre or eclampsia</td>
<td>3800 (1.3)</td>
<td>57 (7.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GDM</td>
<td>13483 (4.6)</td>
<td>48 (6.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pre-existing DM</td>
<td>1429 (0.5)</td>
<td>16 (2.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Obstetrical outcomes

<table>
<thead>
<tr>
<th></th>
<th>No PPCM (N=293674)</th>
<th>PPCM (N=769)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>77559 (26.4)</td>
<td>353 (45.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Induction</td>
<td>80370 (27.4)</td>
<td>270 (35.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mortality (30 days)</td>
<td>18 (0.0)</td>
<td>3 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mortality (2 years)</td>
<td>181 (0.1)</td>
<td>5 (0.7)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Rehospitalization*

<table>
<thead>
<tr>
<th>From 180 days to 1 year post delivery</th>
<th>No PPCM (N=293674)</th>
<th>PPCM (N=769)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2332 (0.8)</td>
<td>59 (7.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>From 180 days to 2 years post delivery</td>
<td>5637 (1.9)</td>
<td>105 (13.7)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* for circulatory diagnoses in a non-gestational period
INHIBITION OF SOLUBLE EPOXIDE HYDROLASE LIMITS MITOCHONDRIAL DAMAGE AND PRESERVES FUNCTION FOLLOWING ISCHEMIC INJURY

Maria K. Akhonkh, Victor Samokhvalov, Feng Hua Yang, Xiuhua Wang, Ratnadeep Basu, Gavin Y. Oudit, Zamaneh Kassiri, Woo Jung Cho, Bruce Hammock, John M. Seubert

Purpose: Cardioprotective effects of epoxyeicosatrienoic acids (EETs) toward acute myocardial ischemia-reperfusion injury have been recognized; however, the precise mechanism(s) are still largely unknown. Our study investigates the protective effects of EETs by inhibiting soluble epoxide hydrolase (sEH), the enzyme responsible for EET metabolism, following surgical occlusion of left anterior descending artery (LAD) of the heart.

Methods: Age matched 2 month old sEH null (KO) and littermate wild-type (WT) mice were utilized in the study, as well C57Bl/6 mice which were administered an sEH inhibitor, trans-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (tAUCB; 10mg/L) or vehicle in drinking water for 4 days prior and 7 days post surgery. Mice from all groups were subjected to surgical occlusion of LAD and cardiac function was assessed by echocardiography prior to and 7 days post surgery. Mice were sacrificed on day 7 and heart tissues were dissected into infarct, peri-infarct (area at risk) and non-infarct (healthy) regions to assess cellular and sub-cellular structure by electron microscopy (EM). Hearts were collected and mitochondrial respiratory enzymes in complexes I, II, III, IV and citrate synthase activities were assayed following MI injury and respiration was assessed using a Clark-type electrode.

Results: Hearts from tAUCB treated and sEH (KO) mice showed significantly improved ejection fraction (p<0.05) and fractional shortening (p<0.05) compared to WT counterparts. Echocardiogram revealed less cardiac remodeling in tAUCB treated and sEH KO groups evident by reduced left ventricular internal diameter (p<0.05) during both systole and diastole. Consistently, EM data showed more intact cardiomyocytes with better arrangement of myofibers and mitochondria in the tAUCB treatment and sEH KO group. Inhibition of sEH resulted in significant improvement in mitochondrial respiration and ETC enzymatic activities. These data suggest EETs have a cardioprotective effect by maintaining mitochondrial integrity and respiratory function.

Conclusion: The inhibition sEH or deletion of sEH gene provides cardiac protection against long-term ischemia, associated with preserved post-ischemic cardiac function and maintaining mitochondrial integrity and respiratory function.

This work was supported by a grant from CIHR (JMS).
CONGENITAL HEART DISEASE HOSPITALIZATIONS IN CANADA: A 10-YEAR EXPERIENCE

Sunjidatul Islam, Yutaka Yasui, Padma Kaul, Ariane J. Marelli, Andrew S. Mackie, Andrew S. Mackie

Background: With improving survival, the prevalence of congenital heart disease (CHD) is rising rapidly in both children and adults. Adults with CHD now outnumber children with CHD. The impact of the growing population of children and adults with congenital heart disease (CHD) on inpatient services in Canada is not known. We sought to assess temporal changes in hospitalizations of CHD patients and predictors associated with longer duration of length of stay.

Methods: We identified all hospitalizations of patients with a CHD diagnosis receiving inpatient care in Canada between fiscal years 2003 to 2012 using the Discharge Abstract Database of the Canadian Institute for Health Information. Poisson regression analysis was performed to assess temporal changes in the annual hospitalization rate. Hospitalization rates were indexed to both the general population and the estimated CHD population of Canada. The hospitalization rate was stratified by children and adult. A multivariable logistic regression with generalized estimating equation model was used to identify factors independently associated with hospital length of stay>14days.

Results: A total of 103,034 hospitalizations occurred in 61,051 CHD patients from fiscal years 2003 to 2012, with an average increase in the number of hospitalizations of 2.4%/year. The absolute number of hospitalizations increased by 4.0% per year in adults and 1.3% per year in children. The greatest increase was in patients aged 65+ (6.5%) followed by those 40-64 years (3.0%). However, the hospitalization rate in adults varied between 39 and 55 per 1,000 CHD population with a reduction of 4%/year (95% CI 0.95 to 0.96, p<0.001). The hospitalization rate in children ranged from 79-87 per 1,000 CHD population and did not change significantly over time (Rate ratio 1.00, 95% CI 1.00 to 1.01, p=0.035). Males accounted for 53.5% of hospitalizations. Predictors of length of stay>14 days were age <1 year, male sex, complex CHD, and hospitalizations associated with both cardiac surgery and catheterization.

Conclusion: The absolute number of hospitalizations with CHD increased over time in both children and adults, with a greater increase in adults. However, the hospitalization rate relative to the CHD population decreased among adults, possibly reflecting improved outpatient management. The absolute increase in CHD hospitalizations will pose a financial burden on health care systems. Adult cardiology programs will need to provide increasing allocation of inpatient health care resources for patients living with CHD.
INVESTIGATION OF A-ANTIGEN SPECIFIC TOLERANCE FOLLOWING ABO-INCOMPATIBLE HEART TRANSPLANTATION (ABOi HTX) USING A NOVEL BLOOD GROUP A TRANSGENIC MOUSE MODEL

Bruce Motyka, Katrina Labonte, Fahim H. Rahman, Jean Pearcey, Kesheng Tao, Michael Mengel, Banu Sis, Peter J. Cowan, Lori J. West

Background: ABOi HTx can be performed safely in infants when ABO antibody levels are low or absent. Following ABOi HTx, immune tolerance develops to the donor A/B antigen(s) by mechanisms not well understood. For further study of ABO-related immunobiology in the transplant setting, we generated transgenic mice (A-Tg, C57BL/6 [B6] background) expressing blood group A-antigen on vascular endothelium, and modeled ‘A into O’ ABOi HTx using A-Tg mice as donors and B6 wild-type (WT) mice as recipients. We previously showed that A-Tg heart grafts undergo antibody-mediated rejection (AMR) in adult WT recipients with preformed anti-A antibodies. We hypothesized that, in contrast, exposure of young WT mice, lacking anti-A antibodies, to A-Tg heart grafts will result in A-antigen specific tolerance.

Methods: WT mice were transplanted at 4 weeks of age with A-Tg hearts (n=16). Serum anti-A antibodies were measured by agglutination assay. Transplanted mice and non-transplanted littermates (n=16) were injected with human A-erythrocytes (A-RBC) at 3-4 months of age. Grafts were assessed by histology for features of AMR.

Results: Anti-A antibodies were detected in only 2/16 transplanted mice at low titre, whereas 8/16 non-transplanted littermates produced anti-A antibodies. Following A-RBC injection, anti-A antibodies were detected in 7/16 transplanted mice, however titres remained low (median titre 1:4). All grafts survived and none showed morphological features of AMR, although five grafts showed focal/diffuse deposition of C4d. In contrast, injection of A-RBC resulted in sensitization of all non-transplanted littermates, inducing high anti-A antibody production (median titre 1:512).

Conclusion: Lack of anti-A antibody production in most transplant recipients compared to non-transplanted littermates, together with failure to effectively sensitize transplanted mice, suggests that exposure of juvenile mice to graft A-antigens resulted in A-antigen specific tolerance. The absence of graft damage in recipients that produced detectable but low titre anti-A antibody suggests combined partial tolerance/graft accommodation. This model will prove useful for addressing mechanisms of tolerance/accommodation in ABOi Tx.
N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE LEVELS IN CHILDREN WITH PULMONARY ARTERY HYPERTENSION

Shine Kumar, Mohammed Eigendi, Long Guo, Prashant Bobhate, Ian Adatia

**Background:** N terminal pro Brain Natriuretic Peptide (NT proBNP) may be a useful biomarker in patients with pulmonary artery hypertension (PAH). We sought to determine whether (NT proBNP) measurements in children with PAH predicted clinical worsening or deteriorating right ventricular function.

**Methods:** We reviewed the records of all children with PAH who had NT proBNP levels measured between 2006-14. We analyzed Panama Functional Class (PFC), Tricuspid Annular Plane Systolic Excursion z score (TAPSE z score), hemodynamic data, need for hospitalization and death.

**Results:** We studied 51 patients with a mean pulmonary artery pressure ≥ 25 mmHg. We excluded 12 patients with a pulmonary artery wedge pressure >15 mmHg. There were 39 patients with PAH (29 males, median age: 50 months; range 1 -195, median height: 109 cm (range 48 -183) and median weight: 15 kg (range 3.1 - 65)). Diagnoses were idiopathic PAH (33.3%), PAH associated with congenital heart disease (51%), pulmonary disease (13%) and pulmonary veno-occlusive disease (2.6%). At baseline the mean right atrial pressure was 5±3 mmHg, mean aortic pressure 64±12 mmHg, mean pulmonary artery (PA) pressure 50±21 mmHg and mean pulmonary vascular resistance index 12.5±6.8 Wood Units.m2. Thirty three patients (85%) had NT proBNP levels measured at diagnostic heart catheterization. Patients with baseline NT proBNP levels > 40.2 pmol/L had higher PFC (3 vs.1.7, p=0.002) and lower TAPSE z score (-2.3 vs. -0.5, p=0.06). Clinical worsening occurred in 13 (33%) patients during mean follow up of 32.4±22.6 months. Children whose clinical deterioration was due to worsening PAH had increased NT proBNP levels (median 154 pmol/L (range 47.9 - 2632) and decreased TAPSE z score (median -3.5 (range -6 to -1.53)) compared with children with non PAH related worsening (median NT proBNP levels 17.5 pmol/L (range 8 - 116.6), p=0.0006) and TAPSE z score (median -0.6 (range -1.87 - +0.24), p=0.015). PFC was higher irrespective of the cause of the clinical deterioration (3.9 vs. 3.2, p =0.16). NT proBNP levels persistently >40.2 pmol/L during clinical deterioration predicted worsening TAPSE z score with 100% sensitivity and 86% specificity.

**Conclusion:** In children with PAH an abnormal NT proBNP level at diagnosis was related to higher functional class and decreased right ventricular systolic function. NT pro BNP levels persistently >40 pmol/L value during clinical deterioration predicted worsening right ventricular function with 100% sensitivity and 86% specificity.
ANGIOTENSIN CONVERTING ENZYME 2 DEFICIENCY RESULTS IN EPICARDIAL ADIPOSE TISSUE INFLAMMATION, CARDIAC INSULIN RESISTANCE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION IN RESPONSE TO DIET-INDUCED OBESITY

Vaibhav B. Patel, Jun Mori, Brent A. Mclean, Nirmal Parajuli, Ratnadeep Basu, Subhash K. Das, Tharmarajan Ramprasath, Josef M. Penninger, Maria B. Grant, Gary D. Lopaschuk, Gavin Y. Oudit

Background: Obesity is increasing in prevalence and is strongly associated with metabolic and cardiovascular disorders. The renin-angiotensin system (RAS) has emerged as a key pathogenic mechanism for these disorders; angiotensin (Ang) converting enzyme 2 (ACE2) negatively regulates RAS by metabolizing Ang II into Ang 1-7.

Methods: We studied the role of ACE2 in obesity-mediated cardiac dysfunction. ACE2-null (ACE2KO) and wildtype (WT) mice were fed a high-fat diet (HFD) or control diet and studied at 6-months of age.

Results: Loss of ACE2 resulted in decreased weight gain, but increased glucose intolerance, epicardial adipose tissue (EAT) inflammation and polarization of macrophages into a pro-inflammatory M1 phenotype in response to HFD. Similarly, human EAT in patients with obesity and heart failure (HF) display a pro-inflammatory M1 macrophage phenotype. Exacerbated EAT inflammation in ACE2KO-HFD mice was associated with decreased myocardial adiponectin, decreased phosphorylation of AMPK, increased cardiac steatosis and lipotoxicity and myocardial insulin resistance which worsened heart function. Ang 1-7 (24 µg/kg/hr) administered to ACE2KO-HFD mice resulted in ameliorated EAT inflammation, and reduced cardiac lipotoxicity and steatosis resulting in normalization of HF.

Conclusion: In conclusion, ACE2 has a novel role in heart disease associated with obesity, where ACE2 negatively regulates obesity-induced EAT inflammation and cardiac insulin-resistance.
SCLERODERMA ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IS ASSOCIATED WITH A HIGH PREVALENCE OF AORTIC STENOSIS

Vikram Gurtu, Adam Kinnaird, Linda Webster, Evangelos Michelakis

**Background:** Aortic stenosis (AS) occurs in 1% of women and 1.6% of men in patients 65-75 years old (Stewart B.F. et al, JACC, 1997), whereas the prevalence of non-bicuspid, non-rheumatic AS in younger patients is lower. While traditional risk factors include hypertension, smoking, renal failure or hyperlipidemia, recent advances implicate inflammation and bone morphogenetic protein (BMP) signaling as pro-calcific factors in aortic valve fibroblasts. Pulmonary arterial hypertension (PAH), and particularly scleroderma-associated PAH (Scl-PAH) includes patients younger than 65, mostly women, that typically do not have traditional AS risk factors but have abnormalities in inflammation and BMP signaling. We investigated the prevalence of AS in a prospective cohort of PAH patients from our clinic, in which the diagnosis is confirmed by multiple tests including invasive hemodynamics and serial echocardiograms.

**Methods:** Over a period of >10 years, we identified a cohort of 116 Scl-PAH and 106 idiopathic (iPAH) patients in which we could analyze serial aortic valve area, peak aortic jet velocity (vmax), and maximum aortic pressure gradient measurements.

**Results:** The age, sex and mean PA pressure in Scl-PAH vs iPAH were: 55.8±1.3 vs 54.9±1.6, 87.1% vs 69.8% females, and 34.8±2.4 vs 49.3±1.6 mmHg respectively. Based on standard echocardiographic criteria, AS (mild, moderate or severe) was present in 13.8% of Scl-PAH and 5.7% of iPAH patients. Moderate-severe AS was 7.8% in Scl-PAH vs 0.9% in iPAH patients. Considering the younger age, female predominance, and absence of traditional risk factors, the high prevalence of AS in Scl-PAH was surprising. To study the rate of progression in this apparently high-risk group, we used another cohort of 50 patients with secondary pulmonary hypertension (sPHT) from left heart disease referred to our clinic (mean age: 70.9±1.7, female 63.3%, mean PA pressure 39.8±2.2 mmHg). These mostly had diastolic dysfunction that at times included mild aortic stenosis. Scl-PAH exhibited much faster progression of AS, with an average yearly increase in vmax of 0.42m/s/year compared to 0.04m/s/year in the sPHT patients (p=0.03).

**Conclusion:** Patients with Scl-PAH may be a previously unidentified high-risk group for AS development, with high prevalence and fast progression rates. The AS risk is particularly high in these younger and mostly female patients considering the absent traditional AS risk factors. Their unique molecular phenotype with high levels of inflammatory cytokines (compared for example to the patients with sPHT), may provide new insights in the pathogenesis of AS. The molecular causes of AS in Scl-PAH may be different than those in iPAH which have higher PA pressures, similar BMP abnormalities, less inflammation, and lower prevalence of AS. Our data suggest a need for increased awareness for AS in Scl-PAH patients, whose serious co-morbidities can complicate the management of AS if its diagnosis is delayed.
NORMALIZATION OF CARDIAC ENERGY METABOLISM PRECEDES
REGRESSION OF LEFT VENTRICULAR HYPERTROPHY AND IMPROVED
FUNCTION IN MICE WITH HEART FAILURE

Nikole J. Byrne, Jody Levasseur, Miranda M Sung, Grant Masson,
Jamie Boisvenue, Martin E Young, Jason Dyck

Background: Impaired cardiac substrate metabolism plays a key role in heart
failure (HF) pathogenesis. Since many of the metabolic changes observed in HF
occur at the transcriptional level of metabolic enzymes, it has been proposed that
impaired cardiac substrate metabolism may be difficult to improve via
pharmacotherapy. However, whether or not the defects in cardiac energy
metabolism that occur in HF are reversible remains unclear. In the current study,
we developed a mouse model of reversible HF and used this to investigate
whether mice with recovered heart function following HF demonstrate improved
substrate metabolism and genetic reprogramming.

Methods: 8-week old, male C57Bl/6 mice were subjected to either sham or
transverse aortic constriction (TAC) surgery to induce HF. Three to four weeks
following surgery mice with severe HF (% ejection fraction <30) underwent a
second surgery to remove the aortic constriction (debanding; DB).
Echocardiography, exercise tolerance, and ex vivo heart perfusion experiments
were performed either without DB (TAC control) or at 1, 3 or 5 weeks following
DB.

Results: Systolic dysfunction (left ventricular end-systolic volume, fractional
shortening, stroke volume, and cardiac output) and diastolic dysfunction
(increased mitral E/A and E/E′ ratios) reversed as early as 1 week post-DB.
Despite showing improvement by 1 week following DB, % ejection fraction
required a full 5 weeks to recover to % ejection fraction of sham mice.
Morphological changes that occur in response to pressure overload, such as left
ventricular (LV) hypertrophy, LV dilation and increased left atrial diameter, also
regressed following DB. Compared to TAC controls that demonstrate impaired
cardiac function and substrate metabolism, all DB mice displayed ex vivo cardiac
function and fatty acid and glucose oxidation similar to sham controls. In addition,
DB completely reversed gene expression of several markers for hypertrophy,
fatty acid oxidation and glucose oxidation that were altered in HF. Finally,
VO2max and exercise tolerance were also recovered by 1 and 3 weeks following
DB, respectively.

Conclusion: Following restoration of the elevated aortic afterload in mice with
severe HF to normal values, molecular and structural remodeling of the heart
was completely reversed. Furthermore, substrate metabolism was restored within
1 week of DB, whereas cardiac function returned to normal by 5 weeks post-DB.
Overall, we show that recovery of impaired cardiac energetics precedes
improved cardiac function, suggesting that recovered heart function relies on
improved cardiac energy metabolism. Our findings have important clinical
implications, as improving cardiac energy metabolism may be essential for the
recovery of heart function in HF patients.
RELATIONSHIP BETWEEN ARTERIAL ACCESS AND OUTCOMES IN A PHARMACOINVASIVE VERSUS PRIMARY PCI STRATEGY IN ST-ELEVATION MYOCARDIAL INFARCTION: INSIGHTS FROM THE STRATEGIC REPERFUSION EARLY AFTER MYOCARDIAL INFARCTION (STREAM) STUDY

Jay Shavadia, Robert Welsh, Anthony H. Gershlick, Yinggan Zheng, Kurt Huber, Sigrun Halvorsen, Philippe Gabriel Steg, Frans Van de Werf, Paul W. Armstrong

Background: The advantage of radial access (RA) for acute coronary intervention in STEMI is predominantly based on primary PCI data. Because limited data exists early post fibrinolysis we examined the relationship between radial versus femoral (FA) access and clinical outcomes in STEMI patients (pts) randomized to a pharmacoinvasive (PI) strategy or primary PCI.

Methods: We evaluated the relationship between arterial access site (chosen locally) and the primary STREAM outcome (30-day composite of death, myocardial infarction, shock and congestive heart failure) and major bleeding according to the treatment strategy received. Propensity score as an inverse probability weight was used in the multivariable analysis.

Results: A total 1820 STEMI pts were included: 895 PI (49.2%) [rescue (n=379, 42.3 %,), scheduled (n=516, 57.7%,)] and 925 primary PCI (50.8%). Irrespective of treatment strategy, there was comparable utilization of either access site (FA: PI 53.4% and primary PCI 57.6%). FA STEMI pts were younger, had more prior hypertension, lesser TIMI risk and more ST-elevation at baseline. The primary composite occurred in 8.9% RA vs. 15.7% FA. On multivariable analysis, the effect favoring RA persisted (OR 0.53 95% CI 0.38 - 0.73, p<0.001). This was especially evident for primary PCI pts (OR 0.42 95% CI 0.27 - 0.67) and a trend existed in PI pts (OR 0.68 95% CI 0.43 – 1.08) (p interaction=0.154, Figure 1). Within the PI strategy, a similar trend favoring RA was evident in both rescue (OR 0.70 95% CI 0.40 – 1.23) and scheduled (OR 0.63 95% 0.26 – 1.54) PCI. There was no overall difference in major bleeding or intracranial hemorrhage with either access group (RA vs. FA 5.8% vs. 6.1%, p=0.77) nor within the PI subgroups.

Conclusion: Regardless of whether a PI or primary PCI strategy is applied during coronary intervention in ST-elevation myocardial infarction, the improved clinical outcomes associated with radial access support this as the preferred arterial access site.
GENETIC VARIATION IN HUMAN CARBOXYLESTERASE 1 (CES1) CONFERS PROTECTION AGAINST NONALCOHOLIC FATTY LIVER DISEASE

Wesam Bahitham, Jihong Lian, Lena Li, Ranadal Nelson, Aducio Thiesen, Richard Lehner

Background: Nonalcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver disease in the Western world. NAFLD is associated with insulin resistance and hyperlipidemia and can progress to non-alcoholic steatohepatitis (NASH). Inactivation of murine carboxylesterase 1d/triacylglycerol hydrolase (Ces1d/TGH) reduces lipogenesis, decreases VLDL production, augments fatty acid oxidation and improves insulin signaling. A number of SNPs have been identified in the human CES1D/CES1/TGH. A SNP in the coding region of the CES1 gene results in G143E amino acid substitution and attenuation of CES1 activity by ~80%. The minor allele frequency of G143E mutation was determined to be 3.7%, 4.3%, 2% and 0% in Caucasian, Black, Hispanic and Asian populations, respectively. The objective of this study was to investigate the effect of CES1/TGH<sup>G143E</sup> on hepatic lipid metabolism.

Methods: Using adeno-associated virus mediated expression of wt CES1/TGH (control), CES1/TGH<sup>G143E</sup> and catalytically dead CES1/TGH<sup>S221A</sup> (negative control) in mice lacking endogenous Ces1d expression. Blood and selected tissues were harvested for further analysis including blood biochemistry, hepatic lipid content, liver histology, insulin sensitivity, and expression of lipogenic and fatty acid oxidation genes.

Results: Metabolic studies provided three distinct alterations in mice expressing CES1/TGH<sup>G143E</sup>: decreased VLDL-TG secretion, decreased de novo lipogenesis and increased fatty acid oxidation leads to reduction of hepatic lipid storage in lipid droplets. These metabolic changes were associated with normal levels of glucose tolerance and insulin sensitivity in mice expressing CES1/TGH<sup>G143E</sup>.

Conclusion: We have developed of an animal model that recapitulates the metabolic phenotype of the allele in human that decreases CES1 activity by 80%, providing a beneficial effect on hepatic lipid metabolism and a potential therapeutic target for hyperlipidemia management.
BASIC SCIENCE POSTERS
ACETYLATION CONTROL CONTRIBUTES TO MATURATIONAL ALTERATIONS IN ENERGY METABOLISM IN NEWBORN HEART

Arata Fukushima, Osama Abo Alrob, Cory S. Wagg, Liyan Zhang, Paul F. Kantor, Ivan M. Rebeyka, and Gary D. Lopaschuk

Background: Dramatic maturational changes in cardiac energy metabolism occur in the newborn period, with a shift in substrate preference from glycolysis to a rapid increase in fatty acid oxidation. The presence of cardiac hypertrophy delays the normal maturation of fatty acid oxidation, which can enhance the susceptibility of the heart to ischemic injury following surgery to correct congenital heart defects (CHDs). Lysine acetylation has been recently identified as a novel post-translational modification involved in the control of cardiac energy metabolism. We therefore examined: 1) the importance of cardiac acetylation in the maturational changes in controlling energy metabolism in the newborn rabbit heart, and 2) if the presence of cardiac hypertrophy alters acetylation control of energy metabolism in the human newborn heart.

Methods: Energy metabolism was measured in 1, 7, and 21-day old rabbit hearts, following which acetylated protein were detected by immunoprecipitation. In addition, right ventricular biopsy samples were collected from neonatal patients undergoing corrective surgery for CHDs, and were stratified according to age and the absence or presence of hypertrophy. These samples were also processed for acetylation status.

Results: Cardiac fatty acid β-oxidation rates were significantly increased in 21-day vs 1-, and 7-day old rabbits (555±26 vs 299±10 and 364±24 nmol.g dry wt-1.min-1, p<0.05). Activities of the fatty acid β-oxidation enzymes including long chain acyl CoA dehydrogenase (LCAD) and β-hydroxyacyl CoA dehydrogenase (β-HAD) were increased in hearts from 7-, and 21-day vs 1-day old rabbits, and were associated with LCAD and β-HAD hyperacetylation. Increased overall myocardial acetylated proteins during maturation were associated with increased expression of mitochondrial acetyltransferase, GCN5L1, while expression of the mitochondrial deacetylase, SIRT3, did not change. Increased expression of the nuclear deacetylase, SIRT1, was accompanied by decreased acetylation of PGC-1α and increased ATP production. Similar to the results of newborn rabbits, there was a maturational increase in overall myocardial protein acetylation following age in non-hypertrophied human newborn hearts. However, this increase in acetylation state was not observed in hypertrophied samples, which was accompanied by an increase in SIRT3 expression and a decrease in GCN5L1 expression.

Conclusion: An increased acetylation of fatty acid oxidative enzymes contributes to the dramatic increase in cardiac fatty acid oxidation rates post-birth. The presence of cardiac hypertrophy prevents the normal increase in myocardial acetylation following birth, resulting in a delayed maturation of fatty acid oxidation.
ACTivating PPARα PREVENTs POST-ISCHEMIC CONTRACTILE DYSFUNCTION IN HYPERTROPHIED NEONATAL HEARTS

Liyan Zhang, Victoria H. Lam, Alda Huqi, Arata Fukushima, Brandon A. Tanner, Arzu Onay-Besikci, Wendy Keung, Paul F. Kantor, Jagdip S. Jaswal, Ivan M. Rebeyka, Gary D. Lopaschuk, Gary D. Lopaschuk

Background: Post-ischemic contractile dysfunction is a contributor to morbidity and mortality following the surgical correction of congenital heart defects (CHDs) in neonatal patients. Pre-existing hypertrophy in the newborn heart can exacerbate this ischemic injury, which may partly be due to a decreased energy supply to the heart as the result of low fatty acid β-oxidation rates in these hearts. We determined whether stimulating fatty acid β-oxidation with GW7647, a peroxisome proliferator activated receptor-α (PPARα) activator, would improve both cardiac energy production and improve post-ischemic functional recovery in neonatal rabbit hearts subjected to volume overload-induced cardiac hypertrophy.

Methods: Volume-overload cardiac hypertrophy was produced in 7-day-old rabbits via an aorto-caval shunt, following which, the rabbits were treated with or without GW7647 (3 mg/kg/day) for 14 days. Hearts were then perfused as biventricular working preparations, and subjected to 35 min of aerobic perfusion, 25 min of global no-flow ischemia, and 30 min of aerobic reperfusion.

Results: Volume-overload cardiac hypertrophy was produced in 7-day-old rabbits via an aorto-caval shunt, following which, the rabbits were treated with or without GW7647 (3 mg/kg/day) for 14 days. Hearts were then perfused as biventricular working preparations, and subjected to 35 min of aerobic perfusion, 25 min of global no-flow ischemia, and 30 min of aerobic reperfusion. GW7647 treatment did not prevent the development of cardiac hypertrophy, but did prevent the in vivo decline in %LVEF typically seen in these volume-overloaded hearts. GW7647 also improved in vitro post-ischemic functional recovery of hypertrophied hearts by 84 ± 6% vs only 56.9 ± 9% in vehicle-treated hypertrophied hearts, n=11, P<0.05). GW7647 treatment also increased cardiac fatty acid β-oxidation rates pre- and post-ischemia, which resulted in a significant increase in overall ATP production. This also resulted in a decrease in post-ischemic proton production due to a decrease in the uncoupling between glycolysis and glucose oxidation. A reduction of nuclear NF-κB, ER stress, as well as an activation of SERCA2 and citrate synthase activity, was observed in GW7647-treated hearts.

Conclusion: PPARα activation of fatty acid β-oxidation in hypertrophied newborn hearts reduces post-ischemic dysfunction and signaling associated with ischemic injury. In immature hearts, stimulating fatty acid β-oxidation may present a novel cardioprotective intervention to limit post-ischemic contractile dysfunction, which may be applicable to in neonatal congenital heart disease repair.
CHF-BAS-1

LIKELY BENIGN? OR LIKELY NOT SO BENIGN: NEWLY IDENTIFIED MUTATIONS IN PHOSPHOLAMBAN

Gareth Armanious, Jessica Gifford, Catharine Trieber, Howard Young, Howard Young

Background: SERCA achieves 70% of the calcium removal from the myoplasm of cardiomyocytes by actively transporting two calcium ions from the myoplasm into the sarcoplasmic reticulum (SR) per hydrolyzed ATP during diastole. During systole, the efflux of the stored calcium from the SR results in the activation of the contractile apparatus of the cardiomyocyte. Reversible inhibition of SERCA by the 52 amino acid SR membrane protein phospholamban (PLB) is crucial to controlling the rate of calcium sequestration, as well as the magnitude of the calcium gradient between the sarcoplasm and myoplasm. This in turn determines the rate of diastole and the force of contraction during systole. Unphosphorylated PLB decreases the apparent calcium affinity of SERCA, while β-Adrenergic-mediated phosphorylation of PLB at S16 by PKA, or at T17 by CaMKII partially restores SERCA activity.

New human mutations in PLB have been recently identified. An A15T mutation was identified in a 4 year old female DCM patient, and a P21T mutation in a 60 year old female patient. Both patients have a family history of DCM. Interestingly, the 4-year-old patient also has a “Likely Benign” mutation in myosin binding protein C3 (MYBPC3) that may contribute to the surprisingly young age of diagnosis. The effects that these variants of PLB have on the kinetics of SERCA, as well as their implications to the regulation of PLB via phosphorylation by PKA is currently under investigation.

Methods: Briefly, recombinantly expressed PLN was purified and co-reconstituted in the presence of SERCA and spectroscopic techniques were used to assess the calcium dependent specific activity of SERCA. The secondary structure of PLN variants was assessed by circular dichroism (CD) in order to correlate structural changes of PLN with altered PLN-SERCA regulatory complex kinetics. Lastly, the ability for these mutants to be phosphorylated by the catalytic subunit of PKA was assessed and the ability of phosphorylated variant PLN to relieve SERCA inhibition was investigated.

Results: The P21T variant of PLN showed increased helical content by CD compared to WT PLN, while the A15T mutation resulted in little to no change in helical content. The inhibitory effects of P21T phospholamban were more potent than those of WT PLN, while the A15T variant of PLN further decreased the apparent calcium affinity of SERCA compared to SERCA in the presence of WT PLN. When these variant of phospholamban were phosphorylated however, their inhibition on SERCA was relieved to a level similar to that of phosphorylated WT PLN.

Conclusion: The A15T and P21T variants of PLN resulted in altered inhibitory characteristics compared to WT PLN when in complex with SERCA. The inhibition of SERCA activity was relieved to varying extents when these variants of PLN were phosphorylated compared to WT. Further analysis of the effects on PKA recognition and the rate of phosphorylation of these PLN mutants is currently under investigation.
POTENTIAL TARGETS AND CONSEQUENCES OF MYOCARDIAL MATRIX METALLOPROTEINASE-2 ACTIVATION IN DOXORUBICIN CARDIOTOXICITY

Brandon Chan, Bryan Hughes, Richard Schulz

Background: Doxorubicin (DXR) is an effective antineoplastic agent used in the treatment of many cancers. However, DXR chemotherapy causes cumulative, dose-dependent cardiotoxicity, leading to heart failure. Chronic treatment causes increased oxidative stress and activation of matrix metalloproteinase-2 (MMP-2). MMP-2 is an extra- and intra-cellular protease that plays an important role in heart disease associated with increased oxidative stress. Intracellular MMP-2 proteolyses several important proteins, including α-actinin, titin, and troponin I, which regulate cardiac contractile function. Intracellular MMP-2 may play a causative role in DXR cardiotoxicity by cleaving specific proteins in cardiomyocytes.

Methods: I investigated whether DXR-induced intracellular MMP-2 activation leads to the proteolysis of confirmed (α-actinin, troponin I) and putative (dystrophin, SERCA2) substrates in cardiomyocytes. Neonatal rat ventricular myocytes (NRVM) were treated with DXR (0.01-1 μM), with or without the MMP inhibitor ONO-4817 (10 μM), for 2-24 h at 37°C. MMP-2 activity in the cell lysates and conditioned media was measured by gelatin zymography. Levels of MMP-2 and its confirmed or putative substrates were measured by immunoblotting. Oxidative stress was measured by changes in mitochondrial aconitase activity. Cell death was measured by lactate dehydrogenase release.

Results: At the concentrations used, DXR did not affect cell viability by lactate dehydrogenase release. DXR increased cellular oxidative stress in a dose- and time-dependent manner as measured by reduced aconitase activity. DXR (1 μM) increased intracellular MMP-2 activity by 1.8 fold and protein level by 1.4 fold after 24 h. DXR increased troponin I levels by 150%, but had no effect on α-actinin. ONO-4817 caused the level of troponin I to trend towards normal in DXR treated NRVM. Ongoing experiments will evaluate intracellular MMP-2 activity by FRET and levels of dystrophin and SERCA2 by immunoblotting.

Conclusion: DXR increases intracellular MMP-2 activity and protein level in NRVM. DXR alters the levels of some intracellular MMP-2 substrates which are critical for cardiac contractile function. Future experiments will study the effect of ONO-4817 on cardiac function, myocardial MMP-2 activity and its substrates in doxorubicin-treated mice. These experiments will help determine whether blocking intracellular MMP-2 activity may be a possible adjuvant therapy to prevent DXR-triggered myocardial injury.
CHF-BAS-3

METABOLIC MODULATION OF THE DISEASED HUMAN LUNG; A TRANSLATIONAL, NOVEL EX VIVO LUNG PERFUSION MODEL

Vikram Gurtu, Roxane Paulin, Adam Kinnaird, Christopher White, Nader Aboelnazer, Darren Freed, Jayan Nagendran, Evangelos Michelakis

Background: Pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF) are deadly pulmonary diseases with limited therapeutic options outside of lung transplantation. Preclinical evidence suggests that suppressed mitochondrial function underlies the pro-proliferative and anti-apoptotic phenotype of pulmonary artery smooth muscle cells and pulmonary fibroblasts, respectively. Two therapies that are known to improve mitochondrial function in vitro and reverse the disease in vivo are a) dichloroacetate (DCA), an activator of pyruvate dehydrogenase (PDH), the gatekeeping enzyme for mitochondrial glucose oxidation, and b) 4-phenylbutyrate (4-PBA), a small molecule that inhibits the endoplasmic reticulum stress (ERS) response, a homeostatic response that suppresses mitochondrial function in times of cellular stress. Although the metabolic response of these drugs can be studied in vitro, their direct effects on the whole human lung may only by studied through ex vivo lung perfusion (EVLP).

Methods: We used a custom EVLP system to study explanted, diseased human lungs of patients undergoing transplant for end stage lung disease from either PAH (n=2), or IPF (n=4). A ventilator was connected to the bronchus and a pump-driven perfusion system (with flow, pressure and temperature sensors connected to a computer) was connected to the pulmonary artery, with the venous efflux re-circulated. The perfusate consisted of modified Krebs-Henseleit buffer or STEEN solution™. Tissue biopsies were collected for analysis of oxygen consumption (using a Seahorse analyzer) and PDH activity at baseline, and after each drug intervention (DCA 5mM and 4-PBA 1g).

Results: In the PAH lungs, hypoxic pulmonary vasoconstriction, a validated marker of lung health, was absent. However administering 0.25mg of treprostinil, a prostacyclin analog used for vasodilation in PAH, resulted in a 31.6% reduction in pulmonary arterial pressure (37.4 to 25.6mmHg), confirming abnormal but present vasoreactivity in the model. In PAH lungs, DCA caused a 61.1% increase in mitochondrial respiration, and a 34-fold increase in PDH activity after 1-hour perfusion. In IPF lungs, PBA increased oxygen consumption by 60.0% ± 10.4%.

Conclusion: We show for the first time that EVLP is a feasible model that can be used to study the direct effects of drugs on diseased, functional human lungs. Lung metabolism and oxygen consumption can be acutely measured in response to candidate therapies such as DCA and 4-PBA, providing supporting mechanistic evidence from animal and human in vitro models. The presence of ventilation and perfusion with normal temperature and blood gas parameters provides a model as close as possible to a living patient. Since before-after biopsies are not possible in clinical trials, this may be a valuable model to facilitate translation of preclinical therapies to clinical trials.
Background: Exercise intolerance and fatigue are symptoms of heart failure (HF) that result from a combination of cardiopulmonary, vascular and skeletal muscle specific effects resulting from poor heart function. We have previously shown that the naturally occurring plant polyphenol, resveratrol, dramatically increases survival in mice with established HF and this occurs in the absence of an improvement in systolic function. Interestingly, resveratrol is known to be an exercise mimetic and exerts multiple beneficial effects on non-cardiac tissues. Based on this, we hypothesized that resveratrol may improve exercise capacity in mice with pressure overload-induced HF via direct effects on the skeletal muscle and vasculature to increase oxidative metabolism and blood supply to the exercising muscle.

Methods: To investigate this, 8-week old male C57/BL6 mice were subjected to sham or transverse aortic constriction (TAC) surgery to induce pressure overload-induced HF. Three weeks post-surgery when mice were in HF (ejection fraction<40%), a cohort of mice from both sham and TAC groups were administered resveratrol (14 mg/day) in their diet. Five weeks following sham or TAC surgery, mice were subjected to endurance treadmill tests, indirect calorimetry using metabolic cages and flow-mediated dilatation of the femoral artery to measure vascular function. In addition, soleus and extensor digitorum longus (EDL) muscles were isolated, permeabilized and O2 consumption was measured in basal- and ADP-stimulated states.

Results: Consistent with resveratrol being an exercise mimetic, mice with HF treated with resveratrol for 2 weeks had increased baseline physical activity levels and significantly improved exercise capacity compared to vehicle treated HF mice (Treadmill duration (min): Sham, 36.64±6.88; TAC, 10.14±1.69 and TAC + resveratrol, 28.30±5.32, p<0.05, n=7-15/group). Consistent with HF inducing direct skeletal muscle dysfunction, ADP-stimulated O2 consumption of isolated EDL and soleus muscle was reduced by ~50% in mice with HF. However, resveratrol restored O2 consumption rates of skeletal muscle fibers similar to that observed in sham mice (p<0.05, n=5/group). HF-induced skeletal muscle insulin resistance was also present in mice as evidenced by impaired insulin-stimulated Akt phosphorylation, which was restored by resveratrol treatment. Furthermore, resveratrol improved flow-mediated vasodilatation of the femoral artery that was impaired in mice with HF, suggesting that blood supply to the hindlimbs may be improved during exercise.

Conclusion: Resveratrol may have direct actions on skeletal muscle and vasculature, independent of cardiac-related effects, to increase exercise tolerance by restoring skeletal muscle mitochondrial oxidative capacity, insulin sensitivity and vasodilatory function. More importantly, our data suggest that resveratrol supplementation may be an effective adjunct therapy for the treatment of HF as it has the potential to improve the quality of life in patients with HF.
Christopher W. White, Shubham Shan, Sanaz Hatami, Vikram Gurtu, Adam Kinnaird, Nader Aboelnazar, Gary D. Lopaschuk, Evangelos Michelakis, Jayan Nagendran, Darren H. Freed

**Background:** Ex vivo heart perfusion (EVHP) has been proposed as a means improving heart preservation and expanding the donor pool. Current clinical EVHP protocols involve preservation in an unloaded and non-working state; however, the impact of this approach on the preservation of donor heart function is unknown. We sought to determine if myocardial load during EVHP impacts the preservation of donor heart function.

**Methods:** Donor porcine hearts were perfused *ex vivo* in a beating state for 12 hours. Loaded hearts (N=4) were perfused in a working mode (left atrial pressure=6 mmHg, heart rate=100 beats/minute) for the entire EVHP interval. Unloaded hearts (N=4) were briefly transitioned into a working mode at hours 1 (T1), 5 (T5), and 11 (T11) for metabolic and functional assessments, but were otherwise perfused in a resting mode (left atrial pressure=0 mmHg).

**Results:** Myocardial function (T11 cardiac index (mL/minute/gram): loaded=6.9±1.0 vs. unloaded=2.0±1.2, p=0.02) and mechanical efficiency (T11: loaded=11±1 vs. unloaded=2±1 %, p<0.01) were better preserved in loaded hearts. Myocardial injury (T11 troponin I (ng/mL): loaded=11.6±0.4 vs. unloaded=12.1±0.3, p=0.39) and edema formation (% weight gain: loaded=14±8 vs. unloaded=24±3 %, p=0.15) did not account for these differences. Free fatty acids were rapidly depleted in both groups (T1 free fatty acid: loaded=4.3±0.4 vs. unloaded=4.1±1.1 mmol/L, p=0.91; T11: loaded=0.18±0.0 vs. unloaded=0.2±0.0 mmol/L, p=0.40); however, triglycerides were continually consumed by loaded hearts and secreted by unloaded hearts (T1 triglycerides: loaded=0.15±0.01 vs. unloaded=0.20±0.03 mmol/L, p=0.13; T11: loaded=0.09±0.03 vs. unloaded=0.39±0.02 mmol/L, p<0.01).

**Conclusion:** EVHP in a loaded state improves the preservation of myocardial function. Uncoupling of fatty acid oxidation may contribute to the decline in myocardial function observed in unloaded hearts; however, further research is required to elucidate the mechanism underlying these observations. These results highlight the need for an EVHP device capable of preserving the donor heart in a physiologic working mode.
CONTROL OF LEFT ATRIAL PRESSURE DURING EX VIVO LUNG PERFUSION: A NOVEL APPROACH

Sanaz Hatami, Christopher W. White, Nader Aboelnazar, Jayan Nagendran, Darren H. Freed

Background: Ex vivo lung perfusion (EVLP) is emerging as a technique for reconditioning and evaluating marginal donor lungs for clinical transplantation utility. Current techniques employ either an open left atrium, where left atrial pressure (LAP) is not controlled, or closed left atrium where LAP is controlled. Currently, closed systems rely on gravity to regulate LAP. We have developed a novel closed EVLP circuit where LAP is regulated by a computer controlled centrifugal pump, permitting a more compact design where reservoir height does not have to be varied to adjust desired LAP.

Methods: Our EVLP platform employs two centrifugal pumps that have been modified to allow computer control of pump RPM. The computer takes input from pulmonary artery pressure and flow sensors, and a left atrial pressure sensor, and then varies RPM to maintain a desired constant pulmonary artery flow (or pressure, user selectable) and constant left atrial pressure. The system was tested utilizing 10 domestic pig lung blocks, perfused with acellular STEEN solution at normothermia.

Results: The figure demonstrates the ability of the system to react to changes in vascular resistance over time. To demonstrate this more effectively, pulmonary vasoconstriction was induced by ventilating the lungs with 100% nitrogen at points A, B and C. As pulmonary vascular resistance increased with the system running in constant pressure mode, the pulmonary artery pump RPM decreased, thereby maintaining constant pressure. Likewise, as flow decreased, the left atrial pump rpm increased to maintain a constant left atrial pressure.
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Conclusion: This novel EVLP platform provides precise regulation of pressure and flow based on user preference, and allows tight regulation of these parameters with minimal input from the user once the settings have been entered.
CYP1B1 INHIBITION ATTENUATES DOXORUBICIN-INDUCED CARDIAC DYSFUNCTION THROUGH MID-CHAIN HETES-DEPENDENT MECHANISM

Zaid H. Maayah, Hassan N. Althurwi, Ghada Abdelhamid, Gabriela Lesyk, Paul Jurasz, Ayman O.S. El-Kadi

Background: Doxorubicin (DOX) is a broad spectrum antitumor drug commonly used to treat different types of cancer. Although DOX has improved survival rates in cancer patients, cardiotoxicity has been reported as a significant side effect. Furthermore, several studies suggested the role of cytochrome P450 1B1 (CYP1B1) and mid-chain hydroxyeicosatetraenoic acids (mid-chain HETEs) in cardiac toxicity. Therefore, we hypothesized that DOX induced cardiotoxicity through the induction of CYP1B1 and its associated mid-chain HETEs metabolites.

Method: To test our hypothesis, Sprague–Dawley rats and human ventricular cardiomyocytes RL-14 cells were treated with DOX in the presence and absence of tetramethoxystilbene (TMS) a selective CYP1B1 inhibitor. Thereafter, cardiotoxicity parameters were determined using echocardiography, histopathology, and gene expression whereas, the level of mid-chain HETEs was quantified using liquid chromatography-electron spray ionization-mass spectrometry.

Results: Our results showed that DOX induced cardiotoxicity in vivo as evidenced by decrease in cardiac output, stroke volume and heart weight/tibial length and change in histopathology, and in vitro in RL-14 cells by induction of β-myocin heavy chain /α-myocin heavy chain (β-MHC/ α-MHC) and cell size. The DOX-induced cardiotoxicity was associated with a proportional increase in the formation of mid-chain HETEs at in vivo and in vitro levels. The direct evidence for the involvement of mid-chain HETEs in the DOX-mediated induction of cardiotoxicity was supported by first; blocking of the DOX-induced cardiac dysfuction as well as the formation of mid-chain HETEs in vivo by TMS, CYP1B1 inhibitor, second; the ability of TMS to inhibit DOX-induced β-MHC/α-MHC and cell size in RL-14 cells. Mechanistically, the protective effect of TMS against DOX induced cardiotoxicity is mediated through the inhibition of mitogen activated protein kinases and nuclear factor-κB.

Conclusion, we provided the first demonstration that DOX induces cardiotoxicity through the formation of mid-chain HETEs in vivo in rat cardiomyocyte and in vitro in RL-14 cells via a CYP1B1-dependent mechanism. Support: This work was supported by a grant from the CIHR to A.O.S.E. Z.H.M. is the recipient of University of Alberta PhD recruiting scholarship.
CVS-BAS-1

COLLABORATIVELY CREATING A SEMI-URGENT PRE-OPERATIVE PATIENT PACKAGE

Mandy Bellows, Lisa Marco

Background: The Cardiology Unit at the Mazankowski Alberta Heart Institute identified a gap in the resources provided to semi-urgent patients and their families. Semi urgent patients discharged home prior to surgery would return for cardiovascular (CV) surgery unprepared. Embarking on a quality improvement opportunity, a collaborative team of front line care providers sought to improve the patient experience. Implemented November 2014, a semi-urgent pre-operative patient package was developed to support patients and staff. The collaborative team designed a checklist to guide staff through the forms, diagnostics, consults, and other preparatory items required completion prior to the patient surgery. Similarly, patient resources included guidance on appropriate shower and skin prep, eating and drinking before surgery, and recovery after heart surgery.

Methods: To determine if the semi-urgent patient package met patient needs, telephone interviews were conducted six months after package implementation. An interview protocol containing nine open-ended questions was used. No demographic information was collected however qualitative responses were documented. Additionally, anecdotal evidence was captured from healthcare providers on the resource impact.

Results: Four interviewees provided feedback, two patients and two patient partners. Patients and their family indicated that the semi-urgent patient package explained integral parts of the CV surgery process (before, during and after surgery). Respondents reported that the resource provided them with the information they needed and contact details if they had questions or concerns. Respondents felt the resource alleviated their anxiety and prepared them for surgery. Staff are satisfied with the semi-urgent patient package and mention that all paperwork and patient preparation is complete preventing early morning delays to the operating theatre.

Conclusion: To fill a patient education and resource gap, the Mazankowski Alberta Heart Institute Cardiology Unit participated in a quality improvement project. Unit staff, clinicians and managers partnered to create an innovative approach for semi-urgent patient education and staff documentation facilitating patient preparedness. Team efforts were reinforced with positive patient, family and staff feedback. The semi-urgent patient package supports quality care and an improved cardiac surgery patient experience.
EX-VIVO LUNG PERFUSION OF DONOR LUNGS: HYPOXIC PULMONARY VASOCONSTRICTION AS A NOVEL INDEX OF LUNG HEALTH

Nader Aboelnazar, Almothana Alzamil, Christopher White, Sanaz Hatami, Evangelos Michelakis, Darren Freed, Jayan Nagendran

Background: The number of donor lungs for transplantation continues to be in shortage, due to the fact that <25% of lungs being donated are accepted for transplantation. Ex-vivo lung perfusion (EVLP) is used to “resuscitate” donor lungs improving their suitability for transplantation. Current assessment of donor lungs on EVLP is primarily based on the P/F ratio (Pulmonary venous pO2/Fraction of inhaled oxygen). Despite adequate P/F ratios, donor lungs continue to develop subclinical injury while on EVLP, limiting clinical EVLP to 4-8 hours. Hypoxic Pulmonary Vasoconstriction (HPV) is the most sensitive sign of health of the lung vasculature as it depends on intact pulmonary endothelial cells and resistance pulmonary artery smooth muscle cells, some of the most damage-susceptible cells in the lung.

Objectives: Identify more comprehensive physiologic measurements to assess lung function pre-transplantation. We hypothesize that HPV is a potentially novel EVLP index and that effective EVLP can reach >12 hours, extending the window for resuscitative targeted therapies (including cell and gene therapies).

Methods: We used a custom-made EVLP system in 8 pig lungs. A ventilator was connected to the trachea and a pump-driven perfusion system (flow, pressure and temperature sensors connected to a computer) was connected to the main pulmonary artery, with the venous efflux re-circulated. The perfusate consisted of STEEN solution™ mixed with blood.

Results: P/F ratios remained acceptable (>400 mmHg) with stable physiologic parameters for >12 hours on EVLP. At 4 hours the lungs demonstrated maximal HPV with an increase in pulmonary vascular resistance (PVR) of 442±27 dyn*s/cm5. However, beyond the 6th hour of perfusion, HPV was blunted. Interestingly, both IL-6 and TNF-α increased in perfusate samples beyond 6 hours of EVLP and continued to increase hourly, in parallel with the decrease in HPV.

Conclusion: HPV is easily demonstratable in EVLP, is apparently a more sensitive index of lung health than the current standard (P/F ratio), and should be used clinically. The decline in the magnitude of HPV corresponds to an increase in inflammation, a well-known inhibitor of HPV. Targeted anti-inflammatory strategies against TNF-α and IL-6 may allow significant extension of the EVLP with direct clinical implications.

MAKING A DIFFERENCE IN THE TRANSITION HOME AFTER CARDIAC SURGERY

Mandy Bellows, Laurianne Gamache-Pearl

Background: The Mazankowski Alberta Heart Institute Cardiovascular (CV) Ward staff identified an opportunity to smooth the patient transition home after cardiac surgery. Staff and clinicians observed patients and family experienced barriers and challenges when being discharged from hospital. The Transition Nurse position was created in March 2013 to support CV surgery patients throughout their post operative care journey. A heightened level of service was made available enabling patients to access community health services more efficiently.

Methods: To determine if the Transition Nurse improved the patient transition home or to an alternate level of care, quantitative and qualitative data were collected. Specifically, the number of Cardiac Rehabilitation Referrals (before and after) and qualitative patient feedback and staff anecdotes were gathered.

Results: Overall, referrals to cardiac rehabilitation increased from 1873 in 2012/2013 to 2236 in 2013/2014 and 2305 in 2014/2015, reflecting a 16.2% and 18.74% percentage gain respectively. Seventy-two hours after discharge patients received a follow up call to assess their health status. Patients reported they experienced uneventful discharges, increased confidence, assistance finding a family doctor and fewer barriers. Upon patient arrival to the unit, the healthcare team is able to identify barriers to discharge facilitating early referral to home care, physician appointments and liaison with community services.

Conclusion: To smooth the patient transition at discharge a Transition Nurse role was created to support patients and their families. In partnership, the patient, family, and healthcare providers identify challenges and barriers to discharge. This all-encompassing perspective improves the patients’ cardiac surgery experience by increasing the quality of services on the CV Ward and access to health services within the community.
DECREASING DEEP SURGICAL SITE INFECTIONS: A COLLABORATIVE ENDEAVOR

Steven Meyer, Alan Sobey, Michele Derbyshire, James Simon, Adam Moon, Teresa O’Gorman, Mandy Bellows

Background: Contributing to an increased length of stay and care costs; a high number of deep sternal infections were observed within the adult cardiovascular (CV) surgery population at the Mazankowski Alberta Heart Institute. Five percent above the National Healthcare Safety Network (NHSN) benchmark for surgical site infections, the Zone Clinical Department Head and Chief of Cardiac Surgery initiated a quality improvement project to review the issue. Supported by an Infection Control Professional and an Improvement Advisor, a collaborative team of health care practitioners from across the CV surgery program were brought together to improve the quality and safety of surgical care at the Mazankowski Alberta Heart Institute.

Methods: The surgical site infection data was analyzed to differentiate between infection types; organ space, superficial sternum, and leg. To understand the cause of the deep surgical site infections the multi-disciplined team used Plan-Do-Study-Act methodology to review the patient journey starting in the same day admission or in house ward unit and progressed to the operating room (OR), CV Intensive Care Unit (ICU) and CV Ward. Process mapping and chart reviews were conducted to provide in-depth contextual knowledge of each patient identified with a surgical site infection. The collaborative team observed the CV surgical journey through multiple innovative methods enabling the identification and removal of multiple vectors of infection.

Results: Several opportunities for improvement were identified in the OR, CVICU and CV Ward. Table 1 provides an overview of the changes made to decrease contamination thought to contribute to infection. As a result, infection rates decreased from 5.3% in Q2 2012/2013 to 0.5% in Q2 2014/2015. A reduction in hospital stays due to infection tapered from 588 days in 2013 to 242 days in 2014. Significant cost savings were also achieved as the CV ward experienced a 55% cost diversion.
ACTIVATORS OF K<sub>Ca</sub> CHANNELS ENHANCE ENDOTHELIOUM-DEPENDENT MODULATION OF NERVE-EVOKED CONSTRICTION IN RAT MESENTERIC ARTERIES

Lunn, Stephanie, S Sandow, TV Murphy, R Wei, PM Kerr, Frances Plane

**Background:** The sympathetic nervous system and the vascular endothelium act in concert to regulate arterial diameter and thus blood flow and pressure. Vasoconstriction triggers a negative feedback response whereby activation of endothelial small (SK<sub>Ca</sub>) and intermediate (IK<sub>Ca</sub>) conductance calcium-activated potassium channels and/or release of endothelium-derived (NO) limit further reductions in vessel diameter. Thus, we have investigated whether small molecule activators of SK<sub>Ca</sub> and IK<sub>Ca</sub> channels can enhance endothelial modulation of nerve-evoked vasoconstriction in the rat perfused mesenteric bed.

**Methods/Results:** N-cyclohexyl-N-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-4-pyrimid-iamine (CyPPA) and naphtho[1,2-d]thiazol-2-ylamine (SKA-31), activators of SK<sub>Ca</sub> and IK<sub>Ca</sub> channels respectively, each caused concentration-dependent, reversible attenuation of nerve-evoked vasoconstriction without altering basal perfusion pressure. Block of NO signaling significantly enhanced nerve-mediated vasoconstriction and prevented the actions of CyPPA but did not significantly affect responses to SKA-31. In contrast, inhibition of transient receptor potential C3 (TRPC3) channels prevented the actions of SKA-31 but was without effect on responses to CyPPA. Selectivity of CyPPA and SKA-31 for SK<sub>Ca</sub> and IK<sub>Ca</sub> channels was demonstrated using apamin and 1-[(2-chlorophenyl) diphenyl methyl]-1H-pyrazole (TRAM-34) respectively.

**Conclusion:** These data indicate different functional roles SK<sub>Ca</sub> and IK<sub>Ca</sub> channels in endothelium-dependent inhibition of nerve-evoked vasoconstriction of mesenteric arteries; SK<sub>Ca</sub> channels appear to be involved in NO-mediated attenuation of vasoconstriction whereas activation of IK<sub>Ca</sub> channels is linked to an NO-independent pathway. The ability of K<sub>Ca</sub> channel activators to suppress nerve-evoked constriction supports the proposal that these channels may provide novel targets for drugs to overcome the endothelial dysfunction and increased sympathetic outflow associated with the development of hypertension.
INVESTIGATION OF THE FUNCTIONAL ROLE OF TRPC3 AND TRPV4 IN ENDOTHELIAL-DEPENDENT MODULATION OF TONE IN RAT MESENTERIC ARTERIES

Ran Wei, Se Lunn, S Sandow, Tv Murphy, Pm Kerr, Frances Plane

Background: Transient receptor potential (TRP) channels contribute to endothelial cytosolic calcium signaling. Roles for both transient receptor potential C3 (TRPC3) and vallinoid type 4 (TRPV4) in agonist-evoked endothelium-dependent vascular relaxation have been proposed. Thus, in this study we have investigated the functional contribution of these channels to endothelium-dependent modulation of phenylephrine- and nerve-evoked increases in tone and to acetylcholine-evoked relaxation in rat mesenteric arteries.

Methods/Results: Using an immunohistochemical approach, TRPC3 and TRPV4 antibodies showed low level diffuse and punctate labeling in endothelial cells and absence in smooth muscle cells. 1-[4-[4,5-(2,3,3-Trichloro-1-oxo-2-propen-1-yl)amino]phenyl]-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (Pyr3), a selective inhibitor of TRPC3 channels enhanced nerve- and phenylephrine-induced increases in tone in endothelium-intact arteries but was without effect on acetylcholine-evoked relaxations. 1-(4-chloro-2-nitrophenyl) sulfonyle-4-benzylpiperazine (RN 1747), an agonist at TRPV4 channels, did not alter vascular tone when applied alone but did enhance endothelium-dependent relaxations to acetylcholine, an effect which was blocked by 3-[(1,4'-bipiperidin)-1'-ylmethyl]-7-bromo-N-(1-phenylcyclopropyl)-2-[3-(trifluoromethyl)phenyl]-4-quinolinecarboxamide (GSK 2193874) a selective inhibitor of TRPV4 channels. However, GSK 2193874 alone did not alter nerve- of phenylephrine-induced responses or acetylcholine-evoked relaxations.

Conclusion: Our findings indicate that TRPC3 channels are involved in endothelium-dependent modulation of smooth muscle contraction but do not appear to contribute to acetylcholine-evoked vasorelaxation. In contrast, inhibition of TRPV4 channels does not appear to alter vascular tone but activation of these channels does enhance vasorelaxation to acetylcholine. Thus, despite showing a similar pattern of endothelial localization, TRPC3 and TRPV4 make distinct contributions to regulation of arterial diameter in rat mesenteric arteries.
IHD-BAS-1

POTENTIAL TARGETS AND FUNCTIONS OF NUCLEAR MATRIX METALLOPROTEINASE -2 IN ISCHEMIC-REPERFUSED HEARTS

Sabina Baghirova, Marcia Y. Kondo, Bryan G. Hughes, Richard Schulz

Background: Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, which are best known to be involved in extracellular matrix remodeling associated with developmental processes and disease progression. The Schulz lab was the first to discover intracellular and intranuclear activity by MMP-2. Several MMPs have been localized to the nucleus since then, however the function and substrates of nuclear MMPs are still unknown. 72 kDa MMP-2 has a C-terminus nuclear localization sequence that is exposed on the protein surface. Lamin A, one possible nuclear MMP-2 target, is part of the intermediate filament protein family and provides structural support to the inner part of the nuclear envelope. We hypothesize that MMP-2 is present in the nucleus under physiological conditions and is activated during oxidative stress, such as during myocardial ischemia-reperfusion (I/R) injury, proteolyzing transcription and DNA repair proteins.

Methods: Rat hearts were isolated and perfused at 37°C with Krebs solution by the Langendorff method aerobically, or subjected to global, no-flow ischemia for 20 minutes, followed by 30 minute aerobic reperfusion in the presence or absence of an MMP inhibitor O-phenanthroline (100µM). Cytosolic, membrane and nuclear fractions were extracted from the rat hearts. Western blots for lamin A (nuclear marker), SERCA2 (membrane marker) and GAPDH (cytosol marker) were used to demonstrate the purity of the nuclear extracts. Changes in nuclear MMP-2 activity was assessed by gelatin zymography, and changes in protein levels of MMP-2 and lamin A were measured by western blot. Immunofluorescence confocal microscopy was used to visualize the distribution of MMP-2 inside the cells. Proteolysis assay was performed by incubating lamin A or B with MMP-2 for 30 minutes at 37°C.

Results: Nuclear fractions had 72kDa MMP-2 activity, western blot and immunofluorescence microscopy confirmed these results. Nuclear MMP-2 activity and levels were increased in rat hearts subjected to ischemia-reperfusion injury. MMP-2 proteolyses the nuclear protein lamin A, but not lamin B, in vitro in a concentration-dependent manner.

Conclusion: Nuclear MMP-2 is present in cardiomyocytes during normal physiological conditions, and is increased during oxidative stress, where it might proteolyse structural support proteins such as lamin A in the nucleus.
ANGIOSTATIN’S HYPOXIC-SPECIFIC EFFECTS ON PRO-MMP-2 AND ENOS IN HUMAN CARDIAC MICROVASCULAR ENDOTHELIAL CELLS

Natasha Govindasamy, Paul Jurasz

**Background:** Coronary artery disease and peripheral artery disease are leading causes of death worldwide. One of the main issues that patients suffering from this disease face is the lack of tissue oxygenation due to poor blood flow that creates hypoxia in tissues. The goal of some therapies is to relieve this hypoxic state by restoring blood flow primarily by increasing collateral angiogenesis. Our lab have shown that an anti-angiogenic mediator, angiostatin, is constitutively produced by human platelets. In hypoxic conditions, angiostatin binds and inhibits ATP synthase on endothelial cell (EC) surfaces and has been associated with inhibition of EC production of MMP-2 and MMP-14 which are important mediators of EC migration and neovascularization. In addition, angiostatin contributes to endothelial dysfunction by inhibiting endothelial NO production via suppression of endothelial nitric oxide synthase (eNOS) in human lung endothelial cells. Overall, its anti-angiogenic effects create a poor microenvironment for neovascularization of ischemic areas, thereby contributing to the pathology of cardiovascular diseases. Our overall objective is to investigate whether angiostatin neutralization using ATP synthase α and β subunits as decoy receptors creates a vascular environment that promotes angiogenesis. However, our current objective is to perform preliminary studies investigating whether angiostatin has similar anti-angiogenic effects on cardiac ECs as observed with lung-derived ECs. We hypothesize that angiostatin will decrease human cardiac EC pro-MMP-2 expression in addition to decreasing eNOS expression under hypoxic conditions.

**Methods:** Primary human microvascular ECs of cardiac origin were treated with angiostatin (600nM), or PBS (control) under normoxic and hypoxic conditions (5% CO₂, balance N₂). Pro-MMP-2 and eNOS expression was measured using Western Blot, and MMP-2 expression was also measured using zymography.

**Results:** Hypoxic ECs treated with angiostatin (61.5±9.6%) had less pro-MMP-2 expression compared to control hypoxic ECs (94.6±26.1%) and normoxic ECs treated with angiostatin (111.9±15.6%, all data normalized to control normoxic ECs, p=0.07). Hypoxic ECs treated with angiostatin (33.5±2.1%) had less pro-MMP-2 gelatinolytic activity compared to control hypoxic ECs (84.5±51.6%) and normoxic ECs treated with angiostatin (73.0±14.1%, all data normalized to control normoxic ECs). Hypoxic ECs treated with angiostatin (38.2±17.8%) also had decreased eNOS expression when compared to control hypoxic ECs (118.7±39.4%) and normoxic ECs treated with angiostatin (73.0±14.1%, all data normalized to control normoxic ECs, p=0.14).

**Conclusions:** Angiostatin decreases pro-MMP-2 and eNOS expression in cardiac ECs, specifically under hypoxic conditions. This may contribute to angiostatin’s anti-angiogenic effects in a hypoxic environment. Ongoing studies will focus on neutralizing angiostatin with treatment of ECs with ATP synthase α, β and δ subunits.
Background: The intracellular activity of matrix metalloproteinase-2 (MMP-2) has been implicated in ischemic heart injury and disease. These pathologies are characterized by both acute and chronic oxidative stress, with mitochondria viewed as a key source of reactive oxygen/nitrogen species (RONS). In vitro, low concentrations of RONS can directly activate intracellular isoforms of MMP-2 via post-translational modifications. We hypothesized that acute, short-term induction of oxidative stress should increase the activity of intracellular MMP-2, in the absence of increased protein levels.

Methods: We investigated whether endogenous RONS produced by pharmacological inhibition of mitochondrial ubiquinol-cytochrome c reductase with antimycin could increase MMP-2 activity in cardiomyocyte and non-cardiomyocyte cell lines. We exposed neonatal rat cardiomyocytes (NRVMs), H9c2 cardiomyoblasts and HT1080 fibrosarcoma cells to antimycin (0.01-1, 0.3-3.2 and 1-100 µM, respectively) in serum-free media for brief (0.5 h) or longer (6 h) intervals to measure changes in MMP-2 activity in cell lysates and conditioned media by gelatin zymography.

Results: The antimycin concentrations used did not affect viability or cell growth, but increased oxidative stress in a dose- and time-dependent fashion as shown by significantly decreased aconitase activity. Antimycin decreased lysate MMP-2 activity in NRVMs, without affecting MMP-2 protein levels. In contrast, antimycin increased MMP-2 activity in H9c2 cells, despite comparable decreases in aconitase activity. HT1080 cells also exhibited increased MMP-2 activities at the lowest concentrations of antimycin used, associated with increased levels of MMP-2 protein. The activity of secreted MMP-2 was not consistently affected by antimycin treatment in any cell line.

Conclusion: We conclude that intracellular MMP-2 activity can be affected by endogenous oxidative stress in cultured cells, dependent upon cell type. This provides further evidence that RONS modulate MMP-2 activity in vivo, independent of changes in protein expression, and could be an important consideration for developing treatments for heart conditions characterized by short-term acute increases in oxidative stress, such as ischemia/reperfusion injury.
IHD-BAS-4

PHARMACOLOGICAL INHIBITION OF SOLUBLE EPOXIDE HYDROLASE PRESERVES MITOCHONDRIAL EFFICIENCY AND CARDIAC FUNCTION POST-MI IN AGED MICE

Kristi Lockhart Jamieson, Victor Samokhvalov, Maria Akhnokh, Xiuhua Wang, Zamaneh Kassiri, John M. Seubert

Background: Cardioprotective effects of epoxyeicosatrienoic acids (EETs) toward acute myocardial ischemia-reperfusion injury have been recognized; however, it remains unclear whether EET-mediated cardioprotection is sustained in the aged population. Our study investigates the protective effects of EETs by inhibiting soluble epoxide hydrolase (sEH), the enzyme responsible for EET metabolism, following surgical occlusion of left anterior descending artery (LAD) in aged animals.

Methods: Age matched 18 month old sEH null (KO) and littermate wild-type (WT) mice were subjected to LAD-ligation to induce myocardial infarction (MI). In parallel, aged C57Bl/6 mice received sEH inhibitor, trans-4-[4-(3-adamantan-1-y1-ureido)-cyclohexyloxy]-benzoic acid (tAUCB; 10mg/L) or vehicle in drinking water for 4 days prior and 7 days post-surgery. Cardiac structure and function was assessed by echocardiography prior to and 7 days post-surgery. Mitochondrial enzymatic activities of respiratory complexes I, II, IV, and citrate synthase were assessed. Respiratory control ratios were determined using a Clark-type electrode.

Results: Hearts from tAUCB-treated mice showed preserved ejection fraction and percent fractional area change compared to WT counterparts. However, no preservation of cardiac function was observed in sEH KO groups. Mitochondrial functions were better preserved following myocardial infarction in hearts from tAUCB-treated and sEH KO mice based on higher respiratory control ratios compared to WT controls. tAUCB treatment increased post-MI enzymatic activity of complex I and II.

Conclusion: Our data suggest that while genetic deletion of sEH showed minor protective effects post-MI, pharmacological inhibition of sEH resulted in sustained mitochondrial bioenergetic efficiency and improved cardiac function.
MICRORNA-301A TARGETS DICER TO ATTENUATE DIFFERENTIATION
OF PRIMARY C-KIT(+) HUMAN ATRIAL CELLS

Alison L. Müller, Darren H. Freed

Background: Cardiac fibroblasts (CFs) and bone marrow-derived mesenchymal progenitor cells (BM-MPCs) both contribute to cardiac fibrosis by differentiating into pro-fibrotic cell types. These pro-fibrotic cells can exacerbate fibrosis by producing excess extracellular matrix proteins that cause the scar to infiltrate viable cardiac muscle that can lead to congestive heart failure. We have previously identified microRNAs (miR) as key regulators of differentiation. These 22-25 nucleotide long non-coding segments of RNA target multiple mRNA transcripts simultaneously to prevent translation of their respective proteins. We found that miR-301a in particular is influential in attenuating the differentiation of both primary CFs isolated from atrial tissue, and primary BM-MPCs, both isolated from patients undergoing open heart surgery. One of the potential targets of miR-301a is Dicer, a protein responsible for processing miRNA and facilitating its inhibitory action. We sought to determine if miR-301a had a similar effect on the recently discovered c-kit+ adult cardiac stem cells (CSCs).

Methods: C-kit+ adult cardiac stem cells (CSCs) were isolated from atrial appendages isolated from patients undergoing open heart surgery. Atrial tissue was digested using collagenase in SMEM media, and then cells were isolated and co-incubated for 2 hrs at 37°C with Dynabeads coated with c-kit antibody. These magnetic beads were washed to remove c-kit- cells, and then remaining c-kit+ cells were plated. At 70% confluency, cells were transfected with miR-301a or scrambled negative control, and then protein and RNA was collected 48hrs later. We performed qRT-PCR and Western blot analysis to investigate Dicer expression and expression of pro-fibrotic markers.

Results: miR-301a transfection of c-kit+ CSCs significantly reduced expression of both Dicer1a and Dicer 1b. In addition, miR-301a over-expression decreased the mRNA level of myosin heavy chain 9, and in the protein levels of non-muscle myosin IIA and alpha-smooth muscle actin.

Conclusion: These results provide insight into a potential cellular mechanism that influences the differentiation of AFs, BM-MPCs, and c-kit+ CSCs which could be caused by changes in Dicer, the key protein in activating micro-RNAs.
LIPMET-BAS-1

CYTOSOLIC CARNITINE ACETYLTRANSFERASE AS A SOURCE OF CYTOSOLIC ACETYL-COA: A POSSIBLE MECHANISM FOR MALONYL-COA REGULATION OF FATTY ACID OXIDATION

Tariq R. Altamimi, Panakkezhum Thomas, Natasha Fillmore, Abhishek Gupta, Liyan Zhang, Gary D Lopaschuk

Background: The roles of carnitine acetyltransferase (CrAT) in regulating cardiac metabolism are poorly understood. In addition to modulation of mitochondrial acetyl-CoA (AcCoA)/Coenzyme A (CoA) ratio regulating pyruvate dehydrogenase-mediated glucose oxidation, we propose that CrAT also provides cytosolic AcCoA for the production of malonyl-CoA, a potent inhibitor of fatty acid oxidation (FAO), and therefore is actively involved in cardiac metabolism of both glucose and fatty acids.

Methods: We performed cellular fractionation followed by total enzyme activity and kinetic studies on wild type (WT) mouse liver and heart tissues and on H9C2 cells to highlight the importance of CrAT in cardiac cell metabolism and to provide evidence for cytosolic localization of myocardial CrAT. Furthermore, to investigate a relationship between CrAT and AcCoA physiology, CrAT activity and immunoblot analysis was performed on cardiac tissue from AcCoA carboxylase 2 knockout (ACC2KO) mice and on WT mice fed, for 10-week, 60% high-fat diet (HFD) then correlated to cardiac levels of short-CoA esters and energy metabolism as compared to respective controls.

Results: Mouse hearts had a significantly higher cytosolic CrAT (cCrAT) activity with lower Km for CoA comparing to their livers (p<0.05) thus emphasising its importance in the production of cytosolic AcCoA. After considering fractionation-induced mitochondrial protein leak, cCrAT accounted for 4.6% of total AcCoA-producing activity. This percentage reached 14.1% and 12.7% in homogenized and digitonin-permeabilized differentiated H9C2 cells, respectively thus confirming CrAT cytosolic localization in cardiac cells. ACC2KO hearts showed decreased CrAT protein expression (p<0.05) and activity (p<0.01) associated with increased AcCoA/CoA ratio (p<0.05) and a tendency toward higher contribution of FAO to ATP production compared to WT controls. Conversely, HFD increased cardiac CrAT expression (p<0.05) and activity (p<0.01) associated with decreased AcCoA/CoA ratio (p<0.05) and significantly reduced glucose oxidation and ATP production rates compared to low-fat diet controls (p<0.05).

Conclusion: A cytosolic CrAT favouring the production of AcCoA exists and supports the ACC-mediated malonyl-CoA synthesis. Further, there is an inverse relation between cardiac CrAT and total AcCoA/CoA ratio as evident in genetically- and physiologically- induced conditions affecting AcCoA/malonyl-CoA control of glucose and fatty acid oxidation. Therefore, CrAT actively regulates cardiac energy metabolism and may represent a therapeutic target in the treatment of heart disease.
LIPMET-BAS-2

A NOVEL ROLE OF EPOXYEICOSANOIDS IN REGULATING CARDIAC MITOCHONDRIA QUALITY CONTROL

Haitham El-Sikhry, Victor Samokhvalov, John Falk, John M. Seubert

Background: Mitochondria are the primary source of energy in cardiomyocytes playing a key role regulating cell survival and function. We and others have previously reported various cardioprotective effects of epoxyeicosatrienoic acids (EETs). EETs are CYP450 epoxygenase metabolites of arachidonic acid that promote pronounced yet poorly characterized cellular effects. In the present study, we investigate the effect of EETs on cardiac mitochondria during starvation induced stress.

Methods: HL-1 cardiac cells were treated with 14,15-EET (1μM) or UA8 (dual acting EET mimetic, 1μM) in serum free starvation buffer for 24 hours. The putative pan-EET receptor antagonist, 14,15-EEZE (10μM), was used as a negative control to confirm EET-mediated effects. Cell survival was assessed using Trypan Blue exclusion assay. Mitochondrial respiration was measured using a Clark electrode. Live-cell imaging was employed to assess alterations in mitochondrial morphology and membrane potential. The 3D mitochondrial morphology and network structure was reconstructed and analyzed by the FilamentTracer module in Imaris software. Electron microscopy was used to observe changes in mitochondrial ultrastructure. Mitochondrial biogenesis was also evaluated.

Results: Starvation induced clear mitochondrial elongation, which correlated with significant reduction in mitochondrial fission proteins DRP1 and Fis1. However, starvation inhibited mitochondrial enzymatic activity and energy production. UA8 preserved mitochondrial respiration and cellular ATP levels. Interestingly, UA-8 treated cells had preserved OPA1 oligomers, mitochondrial cristae density and increased expression the short form of OPA-1. Moreover, EET-mediated events induced SRIT1 activity and DNA-binding activity of pCREB(Ser133) and NRF1/2, suggesting mitobiogenesis.

Conclusion: Together, these initial data suggest that EET-mediated events preserve mitochondrial structure and function during starvation stress, thus promoting cell survival independently from starvation induced mitochondrial elongation.
LIPMET-BAS-3

ELEVATION IN BRANCHED-CHAIN AMINO ACID OXIDATION IS NOT RESPONSIBLE FOR HIGH FAT DIET-INDUCED CARDIAC INSULIN RESISTANCE

Natasha Fillmore, Liyan Zhang, Arata Fukushima, Cory S. Wagg, Gary D Lopaschuk

Background: Obesity is not only characterized by skeletal muscle insulin resistance, but also by cardiac insulin resistance. Recent studies suggest that branched chain amino acids (BCAA) can induce insulin resistance, possibly by inhibiting fatty acid metabolism. For instance, supplementation with BCAA exacerbates high fat diet-induced insulin resistance, increases BCAA oxidation intermediate levels (suggesting elevated BCAA oxidation), and is associated with incomplete fatty acid oxidation in skeletal muscle. However, in the heart, insulin resistance in the setting of obesity is associated with an elevation in fatty acid oxidation. To date, the role of BCAA oxidation in cardiac insulin resistance has not been assessed. We therefore examined the importance of BCAA oxidation in cardiac insulin resistance.

Methods: Mice were fed a high fat diet (HFD) for 10 weeks to induce insulin resistance, and BCAA oxidation, glycolysis, glucose oxidation, and palmitate oxidation rates were measured in isolated working hearts. The perfusate contained 0.8 mM palmitate, 5 mM glucose, 0.15 mM leucine, 0.15 mM isoleucine, and 0.2 mM valine.

Results: The HFD induced cardiac insulin resistance, as evidenced by a dramatic decline in glucose oxidation and a 70% lower insulin-stimulation of glucose oxidation rates in HFD versus low fat diet (LFD) mouse hearts. Interestingly, hearts from the HFD mice also had decreased cardiac BCAA oxidation rates compared to LFD mice (30.8±3.9 vs 55.3±7.1 nmol/min/g dry wt, respectively). BCAA oxidation also was not regulated by insulin, since insulin did not alter BCAA oxidation in either the LFD or HFD mouse hearts. The relative contribution of BCAA to TCA acetyl CoA production in hearts from LFD mice was only 1.3%, while 13.7% of the TCA acetyl CoA originated from glucose oxidation and 85.0% from palmitate oxidation. In HFD mouse hearts, the proportion of BCAA and glucose oxidation to TCA acetyl CoA production decreased to 0.9% and 5.5%, respectively, while the proportion originating from palmitate oxidation increased to 93.6%. Reduced BCKDH expression, a protein involved in BCAA oxidation, in the HFD mouse hearts may contribute to the decline in BCAA oxidation.

Conclusion: These results suggest that in the heart insulin resistance is not due to increased BCAA oxidation and inhibition of fatty acid oxidation. We hypothesize that increased levels of BCAA, due to reduced BCAA oxidation, actually contribute to cardiac insulin resistance by decreasing cardiac insulin signaling via stimulation of the mTOR pathway.
LIPMET-BAS-4

19,20-EDP PROTECTS HL-1 CARDIAC CELLS AGAINST LPS-INDUCED CYTOTOXICITY THROUGH ACTIVATION OF MITOCHONDRIAL FUNCTION AND BIOGENESIS

Victor Samokhvalov, Kristi L. Jamieson, John M. Seubert

Background: Cellular and molecular mechanisms through which epoxy metabolites of long-chain omega-3 polyunsaturated fatty acids ("fish oil") regulate mitochondrial quality control in cardiac cells is unknown. We investigated the role cytochrome P450 epoxygenase metabolites of docosahexaenoic acid, epoxydocosapentaenoic acids (EDPs) in regulation and protection of mitochondria.

Methods: HL-1 cardiac cells were exposed to LPS (1 µg/ml) for 24 hrs, treated with vehicle, 19,20-epoxydocosapentaenoic acid (19,20-EDP, 1 µM) and/or a soluble epoxide hydrolase (sEH) inhibitor trans-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxyl]-benzoic acid (tAUCB, 10 µM), to prevent metabolism. Cell viability, injury, mitochondrial function and biogenesis were assessed.

Results: LPS treatment decreased HL-1 cell viability, contractility, mitochondrial oxidative activity, respiratory control ratios and ATP levels which were attenuated by co-treatment with 19,20-EDP. Examination of cellular ultrastructure via electron microscopy revealed extensive damage and accumulation of aberrant mitochondria in HL-1 cells following LPS treatment. We further explored LPS-triggered mitochondrial damage showing that LPS decreased activities of key regulators of mitobiogenesis, notably pCREB (Ser133), NRF1/ NRF2 DNA binding activities and SIRT1 enzymatic activity. Interestingly, our data demonstrate that 19,20-EDP alone increased the activity of these regulators thereby initiating mitochondrial biogenesis. Furthermore, our results indicate that 19,20-EDP effectively prevented LPS-induced decline in mitochondrial biogenesis. 19,20-EDP also limited LPS-promoted accumulation of aberrant mitochondria. Combining 19,20-EDP with tAUCB potentiated the protective effects against LPS-induced cytotoxicity suggesting that inactivation of she, which effectively prevents degradation of EDPs plays crucial role in producing biological effects.

Conclusion: In summary, our data demonstrated a critical role of DHA metabolites, EDPs, acting as intracellular lipid mediators protecting cardiac cells against LPS-induced injury by regulating mitochondrial function and biogenesis.
LIPMET-BAS-5

19,20-EDP TARGETS MITOCHONDRIAL PATHWAYS TO PRODUCE PROTECTION OF HL-1 CELLS AGAINST HYPOXIA-REOXYGENATION INJURY

Victor Samokhvalov, Kristi L. Jamieson, John M. Seubert

Background: Hypoxia-reoxygenation (H/R) injury promotes extensive damage to cardiomyocyte mitochondria triggering cell death. Recently, we demonstrated that epoxy metabolites of long-chain omega-3 polyunsaturated fatty acids, specifically docosahexaenoic acid (DHA), found in “fish oil” produce potent cardioprotective effects. In this study, we investigated whether the cardioprotective effects of cytochrome P450 epoxygenase metabolites of DHA, epoxydocosapentaenoic acids (EDPs), involve regulating and protecting mitochondria following H/R injury.

Methods: HL-1 cardiac cells were subjected to hypoxia (<1%O2) for 24 hrs followed by 6 hrs of reoxygenation. Cells were treated with vehicle, 19,20-epoxydocosapentaenoic acid (19,20-EDP, 1 µM) and/or a soluble epoxide hydrolase (sEH) inhibitor trans-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (tAUCB, 10 µM), to inhibit enzymatic degradation. Cell viability, contractility, mitochondrial function and biogenesis were assessed

Results: H/R exposure caused a dramatic decrease in contractility and overall cell viability. Furthermore, H/R insult induced a pronounced decline in mitochondrial bioenergetic function such as total mitochondrial oxidative activity, respiratory control ratios and depletion in the levels of ATP. H/R resulted in almost complete downregulation of key regulatory factors required for mitobiogenesis such as NRF1/2, pCREB (Ser133) and SIRT1. The most important finding of this study is that co-treatment with 19,20-EDP resulted in a robust preservation of cell viability, contractility and remarkably, protection of mitochondrial function and biogenesis. We also demonstrated that addition of 19,20-EDP promoted mitobiogenesis under normal conditions and prevented its decline in HL-1 cells after H/R. Addition of 19,20-EDP together with tAUCB greatly potentiated protective effects highlighting an essential physiological relevance of sEH inhibition in EDPs-produced protection.

Conclusion: Our data provide convincing evidence that protective effects of DHA (“fish oil”) may be attributed to the CYP epoxygenase metabolites, EDPs, which regulate mitochondria function and biogenesis.
LIPMET-BAS-6

LDLR-/- MICE LACKING PEMT HAVE ELEVATED TMAO LEVELS BUT ARE PROTECTED FROM HIGH FAT DIET-INDUCED ATHEROSCLEROSIS

Yumna Zia, Ala Al Rajabi, Kelly-Ann Leonard, Catherine Field, Si Mi, Yuan-Yuan Zhao, Jonathan Curtis, René Jacobs

Background: Phosphatidylethanolamine N-methyltransferase (PEMT) is a hepatic enzyme that converts phosphatidylethanolamine into phosphatidylcholine (PC) via three methylation reactions. The PEMT pathway makes 30% of the PC required in the liver and is the only de novo source of choline. PEMT deficient mice are protected against atherosclerosis when bred with either the Ldlr-/- and Apoe-/- mice. PEMT deficiency causes decreased VLDL secretion, plasma LDL levels and homocysteine, which are risk factors for atherosclerosis. Recently, choline supplementation was shown to enhance atherosclerosis in ApoE-/- mice and was dependent on the conversion of choline to trimethylamine (TMA) by the microbial flora in the gut, which was oxidized to trimethylamine N-oxide (TMAO) by hepatic enzymes. In addition, plasma choline and TMAO have been associated with increased risk of CVD in multiple cohort studies. The purpose of this study was to examine the effects of dietary choline supplementation on plasma TMAO levels, and investigate whether choline supplementation eliminates the atheroprotective effect of PEMT deficiency in LDLR-/- mice

Methods: We performed two sets of experiments: In first experiment, 10-12 week old Pemt+/+Ldlr-/- and Pemt-/-/Ldlr-/- mice were fed a chow diet for 12 weeks. In the second experiment, Pemt+/+Ldlr-/- and Pemt-/-/Ldlr-/- mice were fed a 40% high-fat/0.5% cholesterol diet (HFD) supplemented with either 3 or 10 g/kg choline for 12 weeks.

Results: PEMT+/+/Ldlr-/- and PEMT-/-/Ldlr-/- mice do not develop atherosclerosis on chow diet and there was no difference in plasma cholesterol between genotypes. When fed a HFD, PEMT-/-/Ldlr-/- mice are protected against atherosclerosis as compared to PEMT+/+Ldlr-/- mice. Interestingly, choline supplementation did not increase atherosclerosis in the PEMT-/-/Ldlr-/- mice. Plasma cholesterol levels were reduced in PEMT-/-/Ldlr-/-, which did not increase on choline supplementation. Surprisingly, PEMT-/-/Ldlr-/- mice have elevated TMAO levels, which was reduced to control levels by choline supplementation. Furthermore, liver histology showed that PEMT-/-/Ldlr-/- mice developed fatty liver that was improved by choline supplementation.

Conclusion: Choline supplementation does not reverse the protection of PEMT-/-/Ldlr-/- mice against atherosclerosis. PEMT-/-/Ldlr-/- mice have high TMAO levels and fatty liver on HFD. Surprisingly, choline supplementation normalized TMAO levels and reduced the fatty liver. Therefore, plasma TMAO levels are not associated with atherosclerosis but may be a potential biomarker of fatty liver.
TESTOSTERONE MODULATION OF LIPID METABOLISM IN PRE-DIABETES AND POLYCYSTIC OVARY SYNDROME

Gayathri Ananthakrishnan, Spencer Proctor, Mahua Ghosh, Rene Jacobs, Donna Vine

**Background:** The androgen, testosterone, is associated with regulation of lipid metabolism and cardiovascular disease (CVD) risk. Interestingly in males, testosterone is associated with improvements in plasma lipid profile. In contrast, a high plasma level of testosterone in females, such as in polycystic ovary syndrome (PCOS), is correlated with an adverse plasma lipid profile and exacerbated CVD risk. At present we do not know the physiological or mechanistic pathways of how testosterone regulates lipid metabolism under control and disease states such as PCOS. Previous studies from our laboratory have shown that flutamide, an androgen receptor inhibitor, reduces plasma concentration of triglycerides and apoB-lipoproteins, and intestinal secretion of triglycerides in a PCOS rodent model of pre-diabetes and dyslipidemia. The aim of this study was to determine the direct and acute effects of testosterone and dihydrotestosterone on lipid metabolism in control and PCOS-prone rodents. It was hypothesized that testosterone would upregulate intestinal and hepatic lipid and apolipoprotein secretion via AR (androgen receptor)-dependant lipidogenic pathways in control and PCOS conditions.

**Methods:** Control and PCOS-prone/pre-diabetes rodents (JCR:LA-cp, 12 wks of age) were administered vehicle, testosterone propionate (T) or dihydrotestosterone (DHT) (1000ug/kg/d s.c) for 7 days. Following treatment a fasting plasma sample was taken, and then animals underwent a mesenteric lymphatic cannulation procedure to isolate intestinal chylomicrons under fasted (saline) and fed (intralipid) conditions. Plasma and intestinal lymph was analyzed for lipid (triglycerides and cholesterol) and apoB-lipoproteins (apoB48 and apoB100, indicating chylomicrons and VLDL, respectively) using calorimetric and SDS-PAGE methods, respectively.

**Results:** Preliminary data shows plasma free testosterone concentrations were increased 5-7 fold in T treated animals compared to vehicle only, and the relative increase in plasma free testosterone was higher in control compared to PCOS animals. In response to T treatment intestinal lymph triglyceride secretion was increased two fold in fasted conditions and 4 fold in fed conditions in PCOS-prone animals. In contrast no significant effect on intestinal triglyceride secretion was observed in control animals in response to T treatment. Intestinal cholesterol secretion was not affected by T administration in both PCOS-prone and control animals.

**Conclusion:** Our results show intestinal triglyceride, and potentially chylomicron number and size, may be significantly altered in response to testosterone treatment in PCOS-prone and pre-diabetes conditions. Furthermore, this response to T treatment was exacerbated under fed conditions in PCOS-prone/pre-diabetic animals. Our future analyses will further assess plasma and lymphatic apoB-lipoprotein metabolism, and lipidogenic genes involved in testosterone regulation of these pathways. The significance of these studies could be in the clinical translation of the discovery of androgen-receptor specific targets for pharmaceutical or dietary interventions to beneficially modulate lipid metabolism under high androgen-PCOS and pre-diabetes conditions.
Background: Platelets are physiologically involved in hemostasis and wound healing, but can be involved in pathophysiological clot formation, often leading to vascular injury. An important platelet negative-feedback mechanism that limits platelet activation to sites of vascular injury is mediated by nitric oxide (NO) signalling, which acts to inhibit aggregation. NO is generated by endothelial nitric oxide synthase (eNOS) present within platelets. NO acts on soluble guanylate cyclase (sGC), converting GTP to cGMP; cGMP then acts on several downstream mediators to inhibit platelet aggregation. Platelet-secreted factors, such as ADP from alpha granules, have been shown to counteract the effects of exogenous NO on platelets. ADP acts through PI3 kinase to induce platelet aggregation, in antagonism to endogenous NO. However, the effects of ADP on endogenous platelet-derived NO-signalling are unknown. Hence, we hypothesize that platelet-secreted ADP can counteract the endogenous platelet NO-signalling during aggregation.

Methods: Prostacyclin-washed platelet aggregometry in the presence of apyrase (ADPase) and L-arginine (eNOS substrate) was performed to determine the functional effects of ADP on platelet-NO-signalling.

Results: Apyrase (100μg/ml) enhances the negative effects of L-arginine (100μM) on platelet aggregation stimulated by collagen (25.58%±15.59% apyrase and L-arginine under collagen stimulus when normalized to collagen control, N = 7, P<0.05).

Conclusion: Platelet-secreted ADP counteracts the negative-feedback effects of platelet-generated NO.
**VASD-BAS-2**

**ACUTE REDUCTION OF AMBIENT AIR PRESSURE AUGMENTS EFFECTIVE ARTERIAL COMPLIANCE, ENHANCING VASODILATION AND LOWERING SYSTEMIC VASCULAR RESISTANCE IN VIVO**

Anmol Shahid, Michael Sean McMurtry

**Background:** Epidemiologic studies have found lower risk of acute myocardial infarction in humans living at higher elevation even after adjustment for co-morbidities and environmental factors. A potential mechanism for this observation could be reduced compressive force on arteries due to elevation-related reductions in atmospheric pressure. We hypothesized that acute exposure to lower air pressure will enhance arterial vasodilation and effective arterial compliance, reducing systemic vascular resistance in vivo.

**Methods:** **Ex-vivo Pressure Myography:** Second order mesenteric arteries (n=14) were isolated from C57-WT adult male mice and perfused with saline with or without Ca\(^{2+}\) to assess their active and passive properties in a pressure myograph. The system was placed in a barometric chamber allowing manipulation of air pressure and arteries were studied during consecutive acute exposure to three air pressures: 754 mmHg (p0), 714 mmHg (p1) and 674 mmHg (p2). Active vessel responses in the presence of L-NAME and Meclofenamate were assessed with mechanical stepwise manipulation of perfusion pressure (4-140 mmHg) or flow rate (0-70 µL/min). Lumen diameter was measured using a micrometer, with manometers for measurement of pressure drop across the vessel.

**In-vivo Pressure Volume Loops:** Left-ventricular catheterization (closed-chest protocol) was performed on freely breathing anaesthetized adult male C57-WT mice to obtain pressure-volume relationships during consecutive acute exposures to the same three air pressure steps (p0, p1, p2).

**Results:** **Ex-vivo:** Under static conditions, vessel diameters at p1 and p2 increased by 20.9±9.3% and 28.2±8.6% compared to baseline diameter at p0 (p0 vs. p1 and p2; p<0.01). Flow-mediated vasodilation contributed little additional dilation; p0 showed a maximal 67.6±16.08% dilation in response to step-wise increases in flow, whereas p1 and p2 showed flow-mediated dilation responses of 40.0±10.13% and 29.5±7.09, respectively (p<0.05, p0 vs. p2). This observed vasodilation was not diminished in the presence of L-NAME and Meclofenamate. Vascular resistance was statistically significantly reduced at p2 compared to p0 (2.14±0.60 mmHg*min/µL vs. 3.21±0.49 mmHg*min/µL, p<0.05). Perfusion oxygenation was not significantly changed by reductions in air pressure.

**In-vivo:** Total systemic vascular resistance was reduced by acute exposure to lower air pressure (10.09±0.15 mmHg*min/µL at p0 vs. 8.11±1.45 and 8.18±1.24 mmHg*min/µL at p1 and p2, respectively; p<0.05). Significant increases in stroke volume and cardiac output from p0 to p1 and p2 (p<0.05) were also observed.

**Conclusion:** Acute exposure to reduced ambient air pressure increases ex-vivo artery diameter and effective compliance in an endothelium-independent manner, and lowers systemic vascular resistance in vivo. This finding may have translational implications for the epidemiology of and therapy for human cardiovascular diseases.
EFFECTS OF HUMAN PLATELETS ON LUNG CANCER STEM CELL INVASION

Mengjie Yan, Aneta Radziwon-Balicka, Paul Jurasz

Background: [Cancer stem cells (CSCs) are a small subset of cancer cells within a tumor with stem cell-like characteristics and are thought to be responsible for initiating new tumors following metastasis. A number of studies have shown that platelets contribute to cancer cell metastasis, and that factors released from activated platelets stimulate cancer cell invasion, an early step in metastasis, by increasing cancer cell matrix metalloproteinase (MMP) expression. Stromal derived factor-1α (SDF-1α) is a chemokine that is known to increase MMP expression by binding to its receptor CXCR4 and thereby causing the mobilization of both bone marrow and CSCs. Interestingly, platelets contain an abundance of SDF-1α in their a-granules and secrete this chemokine upon activation. However, it is unknown whether the SDF-1α secreted by platelet preferentially stimulates cancer stem cell invasion. Thus we hypothesis that platelets preferentially mobilize cancer stem cell invasion in a SDF-1α:CXCR4:MMP-dependent manner.]

Methods: [Platelet releasates from healthy human donors were collected after collagen-induced aggregation. Flow cytometry was used to identify CSCs within Hoechst 33342-stained A549 human lung carcinoma cells as the Hoechst-negative side population (SP). The MMP-dependent A549 invasion was measured via a modified Boyden Chamber assay in response to platelet releasates. Pharmacological inhibitors AMD3100 and GM6001 were used to investigate the role of SDF-1α-CXCR4-signalling and MMP-dependence during invasion. The stem cell marker CD133 was further utilized to validate the “stemness” of CSCs identified by the Hoechst negative side population.]

Results: [Platelet releasates preferentially promoted invasion by A549 CSCs as measured by the Hoechst-negative SP (4.3 ± 0.3% of total A549 pre-invasion vs. 7.6 ± 0.7% post-invasion, P < 0.05). Neither AMD3100 (10 mM) nor GM6001 (10 mM) significantly decreased CSC invasion as identified by SP. However, AMD3100 significantly inhibited total A549 cell invasion (25.15 ± 8.04 x10^3 cell invaded without vs. 21.38 ± 7.86 x10^3 with AMD3100, P<0.05). Validation of the Hoechst SP as a CSC marker by CD133 staining demonstrated that although CD133 positive cells are enriched in the SP, only 3.84% of Hoechst negative SP cells are also positive for CD133 (1.45 ± 0.59 % in total A549 population vs. 3.84 ± 1.09 % in SP, P<0.05)]

Conclusion: [Activated human platelets preferentially stimulate the invasion of SP-identified cancer stem cells within the A549 human lung carcinoma cell line. Identification of CSC based on both CD133 staining and Hoechst negative SP might be more reliable than using Hoechst SP alone.]
PHARMACOLOGICAL CHARACTERIZATION OF eNOS-BASED PLATELET SUBPOPULATIONS

Gabriela Lesyk, Aneta Radziwon-Balicka, Valentina Back, Maria Jose Santos-Martinez, Marek Radomski, Paul Jurasz

Background: Nitric oxide (NO)-signalling is an important endogenous negative-feedback mechanism that prevents platelet adhesion and aggregation. Recently, our laboratory identified the existence of platelet subpopulations based on the differential ability to produce NO and the presence/absence of endothelial Nitric Oxide Synthase (eNOS-positive and eNOS-negative platelets). We have found that eNOS-negative platelets although less abundant initiate aggregate formation, while eNOS-positives limit aggregate size. Importantly, we have also found that eNOS-negative platelets contain a down-regulated soluble guanylate cyclase (sGC)-Protein Kinase G (PKG)-signalling pathway compared to eNOS-positives, suggesting their refractoriness to NO. If so, this would further support differential roles of these platelet subpopulations in regulating hemostasis/thrombosis. Based on these data, we hypothesized that compared to their eNOS-positive counterparts, eNOS-negative platelets are relatively insensitive to autocrine, paracrine (such as from endothelial cells), and exogenous NO making them ideally suited to initiating hemostatic/thrombotic reactions. To test this hypothesis we studied the effect of exogenous NO-donor S-nitrosoglutathione (GSNO) on eNOS-based platelet subpopulation functionality under flow conditions.

Methods: Prostacyclin-washed platelets were isolated from healthy human volunteers. Platelet functions were assessed by quartz-crystal microbalance (QCM) under flow conditions. This method utilizes piezoelectric effect of quartz crystals and measures change in their resonance frequency corresponding to the mass of adhering material. Platelets were flowed over fibrinogen (100 μg/ml)-coated QCM sensors. Platelets that adhered/aggregated on the sensor surface were then stained, and eNOS and F-actin immunofluorescence was utilized to visualize and quantify eNOS-based subpopulations by laser scanning cytometry (LSC).

Results: In the QCM assay platelet adhesion/aggregation was detected as a decrease in resonance frequency. Platelet samples incubated with GSNO (100 nM) showed impaired aggregation (Δ38±17 Hz) compared to controls (Δ204±40 Hz). ODQ, a sGC inhibitor, abrogated GSNO’s effect causing a decrease (Δ107±27 Hz) in resonance frequency, supporting the fact that NO anti-aggregatory action is sGC mediated. Preliminary LSC experiments enabled visualization of platelet F-actin as red fluorescence and eNOS as green fluorescence on QCM sensors. Compared to controls, the scanned sensors with GSNO incubated platelets showed decrease of both green and red integral fluorescence corresponding to decreased platelet aggregation as detected by QCM. Moreover, GSNO impaired the adhesion/aggregation of eNOS-positive platelets to a greater extent than eNOS-negative platelets, measured by a decrease in the ratio of green/red fluorescence compared to controls.

Conclusion: Preliminary experiments suggest eNOS-negative platelets are less susceptible to inhibition by NO than eNOS-positives. This refractoriness may enable eNOS-negative platelets to initiate hemostatic/thrombotic reactions by being relatively insensitive to platelet or endothelial cell NO compared to their eNOS-positive counterparts.
THE MITOCHONDRIAL DEACETYLASE SIRTUIN 3 (SIRT3) IS IMPORTANT IN THE PATHOGENESIS OF BOTH PULMONARY HYPERTENSION AND PULMONARY FIBROSIS: POTENTIAL FOR AN “OVERLAP SYNDROME” AND A COMMON THERAPY?

Roxane Paulin, Hengjia Zang, Aris Boukouris, Vikram Gurtu, Alois Haromy, Evangelos D. Michelakis

Background: Pulmonary arterial hypertension (PAH) is often associated with interstitial lung disease, like in scleroderma or idiopathic pulmonary fibrosis (IPF). While scleroderma-PAH is considered a part of the PAH umbrella of diseases, including idiopathic PAH, the pathogenesis of IPF (a common and deadly disease) has not been previously linked to PAH. Yet, IPF pulmonary fibroblasts have a very similar pro-proliferative and anti-apoptotic phenotype similar to PAH vascular smooth muscle cells (SMC). As this phenotype is often associated with a cancer-like mitochondrial suppression, we hypothesized that a common mitochondria abnormality may underlie both PAH and IPF. We speculated that the loss of the mitochondrial deacetylase Sirt3, which we recently showed promotes PAH, will also promote IPF.

Methods: We used human lung sections from healthy (unused transplant tissue, n=3) and IPF (transplant recipients, n=7). Sirt3 wild type (Sirt3WT) and knockout (Sirt3KO) mice (n=15 for each) were used in vivo and to isolate pulmonary fibroblasts. IPF was induced both in vitro by bleomycin (BLEO) treatments and in vivo by intra-tracheal delivery of aerosolized BLEO (a standard IPF model).

Results: SIRT3 expression was decreased in human IPF-PH lungs and in Sirt3WT+BLEO lungs and fibroblasts compared to healthy lungs and Sirt3WT. Sirt3KO fibroblasts, like Sirt3WT+BLEO, had decreased mitochondrial function assessed by decreased pyruvate dehydrogenase activity, decreased respiration (Seahorse Assay) and increased mitochondrial membrane potential (TMRM dye in live cell imaging). Sirt3KO and Sirt3WT+BLEO fibroblasts had increased collagen production and smooth muscle actin expression (immunoblot). All of these findings are very similar to those in pulmonary artery SMCs from the same Sirt3KO animals, which develop spontaneous PAH.

In vivo, Sirt3KO mice treated with BLEO developed worse IPF than Sirt3WT+BLEO (dynamic resistance 2±0.5 vs 1.4±0.2cmH2O.s/mL, dynamic elastance 20±3 vs 38±10cmH2O/mL). Intra-tracheal delivery of an adenovirus overexpressing SIRT3 improved both Sirt3KO+BLEO and Sirt3WT+BLEO compared to GFP-only adenovirus. Again, we have previously showed that inhaled gene therapy with the same virus reverses PAH in rodents.

Conclusion: Sirt3 downregulation plays an important role in the development of IPF. While the exact mechanisms by which Sirt3 is downregulated remains to be established, this work opens new perspectives for the treatment of IPF. Given the frequent overlap of IPF and pulmonary hypertension in the same patients, our data suggest the intriguing possibility that they both represent aspects of an “overlap syndrome”, which may benefit from similar therapeutic approaches, despite the differences in the “cell of origin”.

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CLINICAL SCIENCE POSTERS
IS STRAIN RATE A MARKER OF CONTRACTILITY IN CHILDREN?

Silvia Alvarez, Mohammed Alhabden, Michal Kantoch, Joseph Atallah, Timothy Colen, Edythe Tham, Nee Khoo

**Background:** Accurate, non-invasive assessment of left ventricular (LV) systolic function is challenging, with most conventional measures being highly load dependent. Strain rate (SR) derived from speckle tracking echocardiography is a newer measure of ventricular contractility that is relatively chronotropic and load independent with acceptable interobserver reproducibility. There is however, little data on SR performance in children. IVA is a proven non-invasive load-independent measure of LV contractility used in research settings, but remains hampered by poor interobserver reproducibility in clinical trials. This study sought to assess the behavior of SR during tachycardia and inotropic stimulation in children, and compare it to isovolumic acceleration (IVA).

**Methods:** Twenty-four patients (median age, 13.9; range 7.8 - 22.5 years) with no structural and functional heart abnormalities were evaluated under sedation after a radiofrequency ablation (RFA) procedure. Echocardiogram was performed at baseline (B), during atrial pacing (P) and isoprenaline infusion (I). The two latter states are part of standard testing procedure after RFA. Pacing and isoprenaline aimed to achieve 130% of the baseline heart rate (HR). Offline analysis of the echocardiography data assessed global longitudinal SR and lateral wall IVA. We evaluated the percentage (%) change and absolute differences between SR and IVA at baseline, pacing and isoprenaline with paired t-test/paired Wilcoxon test. Additionally, relationships between HR, SR and IVA were assessed. Data are reported as median and ranges.

**Results:** Both IVA and SR increased with pacing and isoprenaline (Table 1). The % change during isoprenaline was greater than in atrial pacing for IVA and SR (p<0.0001). However, IVA showed a greater response in the % change from baseline to atrial pacing than SR (IVA 34.2%, [-15.5 – 141.4] vs. SR 16.2%, [-15.0 – 42.9], p=0.0007). The % change from baseline to isoprenaline infusion state also showed IVA increasing more than SR, but statistically that can only be considered a trend (IVA 130.6%, [-18.6 – 374.1] vs. SR 73.1%, [0 – 328.57], p=0.07) (Fig.1). No significant correlation was observed between IVA, SR and HR.

**Conclusion:** SR is enhanced by inotropic stimulation suggesting SR may be a useful marker of contractility. SR showed a relative insensitivity to changes in HR (abnormal Force-Frequency Relationship) when compared to IVA. The clinical value of SR as a non-invasive assessment of LV contractility warrants further investigation.
CHD-CLIN-2

LEFT VENTRICULAR DIASTOLIC FUNCTION OF THE 6-12 WEEKS HUMAN FETAL HEART: A PROSPECTIVE DOPPLER-BASED STUDY


Introduction: Echocardiographic assessment of the first trimester fetus has become feasible with advances in ultrasound technology. We sought to better understand the evolution of ventricular diastolic function in the first trimester fetus beginning at 6-7 weeks gestational age (GA) using Doppler-based indices.

Methods: 92 prospectively recruited healthy pregnancies were examined by fetal echocardiography at 6-12 weeks GA. Doppler measurements of fetal diastolic function, specifically, mitral valve (MV) E/A wave ratios, mitral inflow duration, and left ventricular (LV) isovolumic relaxation time (IVRT) were examined and grouped into five GA intervals (see table). We examined the relationship between IVRT and inflow duration and fetal heart rate measured as cardiac cycle length (CCL). Statistical analysis was performed using one-way ANOVA to compare the means of these continuous variables across groups.

Results:

<table>
<thead>
<tr>
<th>TABLE</th>
<th>6+0 – 8+0 weeks GA (n=8)</th>
<th>8+1 – 9+0 weeks GA (n=14)</th>
<th>9+1 – 10+0 weeks GA (n=29)</th>
<th>10+1 – 11+0 weeks GA (n=20)</th>
<th>11+1 – 12+0 weeks GA (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>151 (19.4)</td>
<td>169 (10.1)</td>
<td>170 (7.0)</td>
<td>172 (9.8)</td>
<td>162 (5.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>69.4 (24.1) (n=8)</td>
<td>51.7 (21.5) (n=13)</td>
<td>54.5 (12.4) (n=28)</td>
<td>52.6 (9.9) (n=19)</td>
<td>44.3 (14.5) (n=20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IVRT/CCL (%)</td>
<td>14.8 (7.4)</td>
<td>14.3 (5.6)</td>
<td>15.6 (3.6)</td>
<td>15.0 (2.7)</td>
<td>12.0 (4.1)</td>
<td>0.073</td>
</tr>
<tr>
<td>Inflow duration (ms)</td>
<td>98.9 (41.5) (n=8)</td>
<td>81.6 (11.9) (n=14)</td>
<td>98.4 (20.0) (n=28)</td>
<td>104.7 (19.0) (n=19)</td>
<td>145.2 (26.0) (n=20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inflow duration/CCL (%)</td>
<td>22.9 (6.0)</td>
<td>23.0 (3.0)</td>
<td>28.1 (5.2)</td>
<td>29.9 (5.3)</td>
<td>38.9 (6.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Biphasic inflow (%)*</td>
<td>0</td>
<td>14</td>
<td>45</td>
<td>55</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>N/A</td>
<td>0.43 (0.23) (n=2)</td>
<td>0.39 (0.67) (n=13)</td>
<td>0.40 (0.05) (n=11)</td>
<td>0.51 (0.08) (n=19)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All numbers except for % of cases with biphasic flow* are presented as mean ± standard deviation. CCL: cardiac cycle length, N/A: not applicable.

Findings were not linear by weekly intervals, IVRT shortened over the course of the first trimester in its duration but only decreased as a proportion of the cardiac cycle length in the last week. Absolute inflow duration and its proportion of the cardiac cycle length increased with gestational age again with a significant change in the last week. A biphasic LV inflow was never seen prior to 8 weeks but progressively increased in frequency from 8 weeks, becoming uniformly present by 12 weeks. E/A wave ratio among fetuses with biphasic flow patterns were comparable from 8 to 11 weeks increasing only in the last week of the first trimester.

Conclusion: Our findings suggest from 6-12 weeks GA the fetal myocardium improves its diastolic function particularly in the last week which could correspond with the period of compaction of the myocardium. Heart rate may play a role in evolving inflow patterns.
CALCULATING CARDIAC OUTPUT BY SOLVING THE FICK EQUATION USING CARBON DIOXIDE IN CHILDREN WITH PULMONARY HYPERTENSION

Long Guo, Shine Kumar, Jennifer Keis, Andrea Wan, James Coe, Jennifer Rutledge, Ian Adatia

Background: High inspired oxygen concentration (FiO2) with or without inhaled nitric oxide (iNO), is administered to test pulmonary vasoreactivity in children with pulmonary hypertension (PH). VO2 cannot be measured accurately in FiO2 >0.8 in routine clinical practice. It is assumed that VO2 is unchanged during hyperoxia. Our preliminary data suggests that oxygen consumption (VO2) changes substantially in hyperoxia. Carbon dioxide production (VCO2) is easy to measure in hyperoxia. We sought to calculate cardiac output using (VCO2) instead of VO2 during hyperoxia and compared the results with CO measured by thermodilution (TD) in children with PH.

Methods: We measured the VO2 and VCO2 by Mass Spectrometry (AMIS 2000, Innovision, Odense, Denmark) during cardiac catheterization. Cardiac output (CO) was calculated using TD, Fick equation (VO2) and CO2 modified Fick equation (VCO2) in room air (RA) and hyperoxia (FiO2 >0.85 with or without iNO).

Results: We studied prospectively 7 patients without shunts (median age 1.2 years, interquartile range (IQR) 0.9 -8.7, median weight 7.2 kg IQR, 5.1 – 27, BSA median 0.6, IQR 0.3 – 1.0). Mean CO measured in room air was 2.7± 0.96 (TD), 2.2 ± 1.2 (Fick) and 2.1 ± 0.9 L/min (CO2 modified Fick). The correlation between CO measured by Fick and CO2 modified Fick was significant (co efficient 0.86, P=0.013) in RA. In hyperoxia, the mean CO measured by TD was 2.2 ± 1 and 2.6 ± 1.1 L/min (CO2 modified Fick) and correlated well (coefficient 0.9, P = 0.036).

Conclusion: In patients without intracardiac shunts, CO calculated by substituting CO2 in the Fick equation correlated well with CO measured by TD in room air and in hyperoxia. If VCO2 is measured, solving the Fick equation for CO2 may be a practical alternative to calculate CO in hyperoxia in situations where TD is unavailable or inaccurate.
HOSPITAL READMISSION OF CONGENITAL HEART DISEASE PATIENTS IN CANADA

Sunjidatul Islam, Yutaka Yasui, Padma Kaul, Andrew S. Mackie

Background: Hospital readmissions represent a vast burden on health care resources and in many cases are avoidable. However, little is known about hospital readmission in children or adults with congenital heart disease (CHD) in Canada. We assessed readmission rates among CHD patients stratified by age, sex, and severity of CHD from 2003 to 2012 in Canada and identified risk factors associated with hospital readmission.

Methods: A retrospective cohort study was conducted among CHD patients identified from the hospital discharge abstract database of the Canadian Institute for Health Information from 2003 to 2012. We identified all index hospitalizations and followed them for up to 12 months to determine the readmission rate. The readmission rate for a given period of time, which is a cumulative outcome, was determined using a Poisson regression model and also stratified by age, sex, and severity of CHD. Multivariable logistic regression analyses were performed to identify risk factors associated with readmission within 2 weeks and 1 month after discharge.

Results: The readmission rates per 1,000 CHD patients were 48 within 2 weeks, 83 within 1 month, 163 within 3 months, and 353 within 1 year. More adults were readmitted compared to children (5.4% vs. 4.2% at 2 weeks and 8.5% vs. 7.2% at 1 month). Patients age ≥ 65 years had a 1.4 to 1.8 times higher readmission rate compared to infants (p<0.001). Among children, infants showed significantly higher readmission rate at 2 weeks (p=0.014), 1 month (p=0.03) and 3 months (p<0.001). The readmission rates were 2.5 to 4.9 times higher in complex CHD patients (p<0.001) and 1.3 to 1.8 times higher in moderate CHD patients (p<0.001) than simple CHD patients. Independent risk factors for readmission within 2 weeks and 1 month were age ≥ 40 years, age < 1 year, male sex, longer index hospitalization stay, and complex CHD. In adults non-CHD cardiovascular diagnoses (congestive heart failure, atrial fibrillation and flutter, aortic valve disease, ischemic heart disease) were the most common diagnoses associated with hospital readmission while in children ventricular septal defect and respiratory illness were the most common reasons for readmission.

Conclusion: Hospital readmission was common in CHD patients, particularly adults aged 40+ years, infants, males and those with complex lesions. Further studies are required to investigate the mechanism for unplanned readmission.
INDUSTRIAL DEVELOPMENTAL TOXICANT EMISSIONS AND CONGENITAL HEART DISEASE IN URBAN AND RURAL ALBERTA, CANADA

Ngwezi DP, Hornberger LK, Serrano-Lomelin J, Fruitman D, Osornio-Vargas A, Hornberger LK

**Background:** Our previous results suggested a spatio-temporal association between mixtures of organic compounds and congenital heart disease (CHD) in Alberta. This time we sought to explore for differences in associations in the urban and rural areas of Alberta.

**Methods:** The Principal Component Analysis matrix derived for the Alberta Province, was scaled down to urban and rural regions to obtain the corresponding mixtures of developmetal toxicants (DTs). Similarly crude CHD rates for urban and rural areas were calculated.

**Results:** There were strong positive correlations between mixtures of organics and gases and urban CHD rates, $r=0.74$, $p=0.03$ and mixtures of organics only and rural CHD rates, $r=0.80$, $p=0.02$.

**Conclusion:** Overall the organics are positively correlated with CHD rates and the difference being the urban CHD rates which are associated with the mixture containing gases. This may point to different industrial activities in urban and rural settings.
CHD-CLIN-6

STRESS PERFUSION MAGNETIC RESONANCE IMAGING TO DETECT CORONARY ARTERY LESIONS IN CHILDREN

Chodchanok Vijarnsorn, Dion Pepelassis, Daryl Schantz, Michelle Noga, Edythe B Tham

Background: Stress perfusion cardiovascular magnetic resonance (CMR) has been used widely in adult ischemic heart disease, but data in children is limited. We sought to evaluate the feasibility and diagnostic accuracy of stress CMR in children in our institution.

Methods: Stress perfusion CMR was performed on a 1.5T Siemens Aera scanner using echo-planar imaging with motion correction. Wall motion abnormalities and the presence of late gadolinium enhancement were also noted. Correlation was made between stress CMR and coronary angiogram (CAG) or nuclear study when available. Clinical follow-up at 1 year was noted for prognosis of stress CMR.

Results: We reviewed 33 stress perfusion CMR studies in 22 children (4 months – 18 years old) using adenosine in 28 (84%) and dipyridamole in 5 (16%). Indications for stress CMR included 6 post arterial switch operation, 4 Kawasaki disease, 4 post anomalous coronary artery repair, 3 surveillance for post heart transplant vasculopathy, 3 with chest pain, 1 post LCA stent and 1 dilated cardiomyopathy. Nine studies (27%) in children <8 years were performed under sedation using Of 33 studies, 19 (58%) studies from 15 (68%) patients showed normal perfusion. Matched perfusion defects with positive late enhancement and wall motion abnormalities were found in 7 studies (3 patients) while 4 studies (2 patients) showed inducible ischemia. In 9 studies compared to available CAG, MIBI or CTA, the accuracy of stress CMR was 67% with a negative predictive value (NPV) of 75%. Two unsedated patients aged 9 & 10 years were uncooperative during the CMR due to the tachycardic effect of adenosine, which led to 1 false negative result. Taking into account the clinical follow up at 1 year, the positive predictive value and NPV of the stress CMR were 65% and 96% respectively, with a specificity of 85% and sensitivity of 86%. The likelihood ratio was 12.4 (p < 0.001).

Conclusion: Stress CMR correctly identifies 85% of patients who do not have a cardiac ischemia at 1 year follow up. The high NPV (96%) indicates that a negative stress CMR is a reassuring result for absence of significant coronary artery lesions. Use of stress CMR as a complement to conventional CAG to rule out obstructive coronary disease in pediatric population seems recommendable however the efficiency requires larger cohorts.
CHF-CLIN-1

SERUM METABOLOMICS REVEAL A DISTINCT FINGERPRINT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Beshay Zordoky, Miranda Sung, Justin Ezekowitz, Rupasri Mandal, Beomsoo Han, Trent Bjorndahl, Souhaila Bouatra, Todd Anderson, Gavin Oudit, David Wishart, Jason Dyck

Background: Heart failure (HF) with preserved ejection fraction (HFpEF) is increasingly recognized as an important clinical entity. Preclinical studies have shown differences in the pathophysiology between HFpEF and HF with reduced ejection fraction (HFrEF). Therefore, we hypothesized that a systematic metabolomic analysis would reveal a novel metabolomic fingerprint of HFpEF that will help understand its pathophysiology.

Methods: Ambulatory patients with clinical diagnosis of HFpEF (n = 24), HFrEF (n = 20), and age-matched non-HF controls (n = 38) were selected for metabolomic analysis as part of the Alberta HEART (Heart Failure Etiology and Analysis Research Team) project. 181 serum metabolites were quantified by LC-MS/MS and 1H-NMR spectroscopy.

Results: Compared to non-HF control, HFpEF patients demonstrated higher serum concentrations of short-chain, medium-chain, and long-chain acylcarnitines, carnitine, creatinine, betaine, and several amino acids; and lower levels of phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins. Long-chain acylcarnitines, 2-hydroxybutyrate, 3-hydroxybutyrate, and acetate were found to be higher in the HFpEF group than the HFrEF group, while sphingomyelin (C24:1), some phosphatidyl cholines and Lysophosphatidyl cholines were found to be lower in the HFpEF group than the HFrEF group.

Conclusion: The metabolomics approach employed in this study identified a unique metabolomic fingerprint of HFpEF that is distinct from that of non-HF controls and from patients with HFrEF.
THE FACTORS ASSOCIATED WITH NATRIURETIC PEPTIDES (BNP AND NT-PROBNP) TESTING IN PATIENTS PRESENTING TO EMERGENCY DEPARTMENTS OF ALBERTA WITH SUSPECTED HEART FAILURE

Nariman Sepehrvand, Jeffrey A. Bakal, Meng Lin, Finlay A. Mcalister, James C. Wesenberg, Justin A. Ezekowitz

**Background:** Testing for natriuretic peptides (NP) such as BNP or NT-proBNP in the emergency department (ED) adds to the diagnostic accuracy when evaluating patients for acute heart failure (HF). The aim of this study was to investigate factors related to the testing of NPs in the ED, which were rolled out to all Alberta EDs in 2012.

**Methods:** Data from all adult patients in Alberta attending the ED, incorporating linked administrative data including clinical visits to the ED or hospital, mortality and laboratory data from 2012 to 2013, was used. Patients with or without HF were included if they had testing for a NP in the ED and a comparator group of patients with HF but no NP testing were also included. For patients with multiple ED visits, only the first visit was included. A series of logistic regression models were created to adjust for key covariates on outcomes as well as likelihood of having NP tested.

**Results:** Of the 16223 patients in our cohort, 5793 were patients with HF (n=3148 tested for NPs and n=2645 not tested) and 10430 were patients without HF but tested for NPs (See Table). In the group without HF who were tested for NPs, the main diagnoses were diseases of the respiratory system (34%), non-HF cardiovascular diseases (13%), signs and symptoms suggestive of respiratory or circulatory diseases NYD (17%), and others (34%). Patients with HF who were tested had a higher rate of hospital admission compared to those who were not tested (78.4 vs. 62.2%; p<0.001). Repeat ED visit rates were lower among patients with HF who were tested for NPs compared to those who were not (p<0.02), but there was no re-hospitalization or mortality difference between these two groups. Among patients with HF, being male, an urban resident, having prior HF, being seen by an emergency medicine or cardiology specialist and being in hospitals with medium ED visit volumes were associated with increased likelihood of testing for NPs.

**Conclusion:** Several factors, including the type of provider and ED clinical volume, influenced the utilization of NPs in routine ED practice. NP testing was also associated with fewer repeat ED visits and a higher likelihood of being admitted to hospital. Optimization of a NP testing strategy in clinical practice would be useful for healthcare systems.
BETTER TOGETHER: BOOKING THE OR COLLABORATIVELY

Mandy Bellows, Tara Peters

Background: Within the Cardiac Surgery program in Edmonton, Alberta, an innovative approach was needed to reduce cardiac surgical postponements in a climate of finite operating room time, fiscal restraint and growing waitlist. The cardiac surgical slate, booked by several Surgeons’ Offices using an individualized approach, lacked an omniscient perspective; one that is cognizant of case mix, procedure complexity and bed availability within the Cardiovascular Intensive Care Unit (CVICU) and Cardiovascular Ward. Postponing surgeries can cause undue physical and psychological stress to patients and families. To improve the patient experience and care quality, a cost neutral, synergistic approach was applied.

Methods: The Cardiovascular Surgery Collaborative Booking Team was born. A strategic alliance of Nurse Navigators, Unit Managers, Surgeon’s Administrative Assistants, and Cardiac Operating Room (OR) and Zone Program Nurse Managers met weekly to plan the next week’s slate. This Team discussed and made adjustments to the draft slate, planning for complex cases, potential unplanned emergencies and patient flow.

Results: Bringing stakeholders together and fostering shared decision making decreased postponements due to “no beds” from 13.6% to 2.0%. Additionally, patient arrival to CVICU “delay-time” decreased from 1120mins to 400mins. Added benefits of the collaborative team approach include building relationships with adult congenital patients and families prior to surgery and increased OR utilization.

Conclusion: As a result of this constructive way to increase communication and collaboration among members of the adult cardiac surgical program, the pediatric cardiac surgical program has initiated a similar group dedicated to the same purpose. Advocating for patients and families is at the heart of what we do and we are better able to do so by enhancing relationships.
OPTIMIZING PREOPERATIVE HEMOGLOBIN IN ADULT ARDIAC SURGERY USING INTRAVENOUS IRON SUCROSE: A CASE SERIES STUDY

Abdelsalam M Elhenawy, Linda J Carroll, Sean M Bagshaw, Steven R. Meyer

**Background:** Preoperative anemia is a common and potentially serious hematological problem in elective cardiac surgery and increases the risk for perioperative red blood cell (RBC) transfusion. Transfusion is associated with postoperative morbidity and mortality. Preoperative intravenous (IV) iron therapy has been proposed as an intervention to reduce perioperative transfusion.

**Objectives:** To investigate the effect of preoperative IV iron sucrose treatment on preoperative hematimetric parameters (hemoglobin [Hb] and ferritin level), perioperative RBC transfusion, and outcomes.

**Method:** Retrospective observational study carried out in our institution between January 2010 and December 2014. The study included patients with iron deficiency anemia scheduled for elective cardiac surgery and treated with intravenous iron sucrose alone. Treatment efficacy was analyzed based on the Hb increase from baseline to just before surgery.

**Results:** A total of 27 patients received IV iron sucrose with an average dose of 589 mg (range: 300-1000mg) of IV iron sucrose. After IV iron treatment, hemoglobin increased by 8% from 128 ± 9 mg/dL to 138 ± 7 mg/dL (p = 0.5, 95% CI, 5.8-15.0). Serum ferritin increased significantly from 39 ± 60 ng/ml to 148 ± 108 ng/ml (p = 0.004, 95% CI, 61-157). Perioperative RBC transfusion was reduced markedly from 40% (our institution’s transfusion rate) to 22%.

**Conclusions:** In patients with preoperative iron deficiency anemia, IV iron sucrose therapy showed a modest increase in the hemoglobin level. It was associated with significant increase in ferritin levels and marked reduction in RBCs transfusion compared with the overall transfusion rate for our institution.
EUROSCORE II IS SUPERIOR TO STS AND EUROSCORE I IN PREDICTING OPERATIVE MORTALITY IN OCTOGENARIANS FOR ISOLATED CORONARY ARTERY BYPASS GRAFTING SURGERY

Jessica G.Y. Luc, Sadek Al Shouli, Michelle M Graham, Colleen M Norris, Yugmel Nijjar, Steven R Meyer

Background: Octogenarians represent an increasing proportion of cardiac surgical candidates. Despite the availability of different risk-scoring algorithms, the use of these models is not well established in octogenarians. The objective of this study was to compare the recently introduced EuroSCORE II (ES II) with its previous version EuroSCORE I (ES I) and the STS risk score in predicting operative mortality in patients 80 years of age and older undergoing isolated coronary artery bypass grafting surgery (CABG).

Methods: This retrospective analysis included all patients age 80 and older (n=304) and a randomly selected group under age 80 (n=608 of 4732) who underwent isolated CABG at our institution from 2002-2008. Accuracy in predictive ability of the STS, ES I, and II was assessed by plotting the areas under the receiver operator characteristic (AUROC) and comparing the observed and predicted operative mortality for the two groups.

Results: Compared to controls, patients age 80 and older were more likely to have standard predictors of perioperative complications including renal impairment (creatinine 65 vs. 54; p=0.01), female gender (26% vs. 15%; p<0.001), emergency surgery (4% vs. 3%; p<0.001), chronic lung disease (14% vs. 11%; p<0.001) and reduced left ventricular function (45% vs. 56%; p<0.001). Patients age 80 and older had a significantly higher predicted mortality by STS Score (3 ± 2% vs. 1 ± 1%; p<0.001), additive ES I (8 ± 3% vs. 4 ± 3%; p<0.001), logistic ES I (15 ± 14% vs. 5 ± 6%; p<0.001), and ES II (4 ± 3% vs. 2 ± 2%; p<0.001). Observed mortality was 1% and 2% for patients under and over age 80, respectively (p=0.323). AUROC revealed areas for STS, additive and logistic ES I and ES II, respectively, for patients under age 80 (0.829, 0.750, 0.785, 0.845) and age 80 and over (0.671, 0.709, 0.694, 0.794) [Figure].

Conclusion: ES II demonstrates better discriminatory accuracy for predicting operative mortality than ES I and STS Score in patients age 80 and older undergoing isolated CABG. However, the predictive ability of all scores assessed was still inferior for patients age 80 and older compared with patients under age 80. New specific validated risk-algorithms will allow for more accurate prediction of true operative mortality risk in octogenarians.
CVS-CLIN-4

TRANSCATHETER VALVE-IN-VALVE: A CAUTIONARY TALE

Jessica G.Y. Luc, Miriam Shanks, Benjamin G. Tyrrell, Robert C. Welsh, Steven R. Meyer

Background: Transcatheter aortic valve replacement (TAVR) by valve-in-valve (VIV) implantation is an excellent option for patients with a degenerating aortic bioprosthesis for whom conventional aortic valve replacement (AVR) is deemed too high risk. The TAVR VIV is anchored by virtue of friction and oversizing. Thus, the exact internal diameter of a degenerated bioprosthesis is essential for valve sizing. We describe the first case of valve-in-valve transapical TAVR involving a 29 mm Edwards Sapien XT valve into a 29 mm failing Medtronic Freestyle stentless bioprosthesis.

Methods: An 82-year-old gentleman with prior aortic root replacement with a 29 mm Freestyle stentless bioprosthesis and concomitant coronary artery bypass grafting surgery presented 4 years later with severe New York Heart Association grade IV dyspnea. Transesophageal echocardiogram (TEE) revealed a degenerated Freestyle stentless bioprosthesis with a ruptured left coronary cusp resulting in severe transvalvular aortic regurgitation, a mean aortic gradient of 7 mmHg, 30 mm aortic root diameter, 36 mm ascending aorta diameter, and preserved ventricular function. By echocardiography, the bioprosthetic annulus size was estimated to be 26x27 mm, consistent with previously reported manufacturer's data. AVR and TAVR VIV were considered. Given the patient’s age, multiple comorbidities and patent bypass grafts, the transcatheter approach was deemed the most appropriate method to address this gentleman's prosthetic valve dysfunction. A transapical approach was chosen to optimize deployment of the prosthesis due to the presence of peripheral vascular disease and distorted sinotubular junction anatomy.

Results: A 29 mm Edward Sapien XT valve was chosen for TAVR VIV therapy in accordance with the predicted 27 mm internal diameter of the 29 mm Freestyle prosthesis. Following deployment of the valve as guided by TEE and fluoroscopy into an excellent position, the valve embolized distally towards the aorta. The valve was retrieved, reloaded by inflating the balloon and reimplanted into an excellent position. However, the valve proceeded to migrate into the ventricle along the guidewire. The patient underwent emergent open-heart surgery during which the Edward Sapien XT valve was surgically retrieved from the left ventricle. Intra-operative findings revealed that the inner dimension of the Freestyle stentless bioprosthesis was grossly dilated to greater than 30 mm in diameter, which was much larger than the 27 mm internal diameter anticipated. Conventional AVR with a St. Jude Trifecta valve was uncomplicated with excellent post-operative hemodynamic results.

Conclusion: We describe the first case of TAVR VIV involving a 29 mm Edwards Sapien XT valve into a large 29 mm failing Freestyle stentless bioprosthesis. Unanticipated dilation of the Freestyle prosthesis resulted in intra-procedural embolization of the Edwards Sapien XT valve necessitating urgent conversion to conventional AVR. Our experience suggests that TAVR VIV with the 29 mm Edwards Sapien XT valve in the setting of a degenerated 29 mm Medtronic Freestyle stentless bioprosthesis may not be an optimal therapy for all.
THE Sgarbossa CRITERIA: STILL USEFUL IN 2015?

Debraj Das, Brent M. McGrath, Evan Lockwood

**Background:** First reported in 1996, the Sgarbossa criteria were developed to detect an acute myocardial infarction (AMI) in the setting of an endocardial right ventricular paced rhythm or left bundle branch block (LBBB). The Sgarbossa criteria include: ST-segment elevation of ≥ 1 mm concordant with the QRS complex in any lead (score of 5), ST-segment depression of ≥ 1 mm in lead V1, V2, or V3 (score of 3) and ST-segment elevation of ≥ 5 mm discordant with the QRS complex (score of 2). Here we discuss a case of an adult male with a previously implanted single-chamber pacemaker for third degree heart block who presents with cardiac chest pain.

**Methods:** A 63-year-old male with a history of smoking, hypertension, and diabetes mellitus presented to the emergency department with a four-hour history of severe central chest pain. His baseline ECG had a ventricular paced rhythm. On presentation, his ECG revealed >5mm discordant ST elevation in V2 and V3 and >1mm concordant ST elevation in lead V4 satisfying two out of three Sgarbossa criteria.

**Results:** Although modifications to the original Sgarbossa criteria have been suggested, it remains an essential tool for rapid diagnosis of AMI in paced or LBBB rhythm. Smith et al. have proposed a different third criterion to improve overall sensitivity. By replacing ST-segment elevation ≥ 5 mm discordant with the QRS complex with an ST/S ratio less than -0.25, there was improvement in diagnostic utility. However, this modification is not widely used in clinical practice and has not been validated in paced rhythms. Moreover, Tabas et al. have validated the original Sgarbossa criteria in a meta-analysis and it remains very applicable given its high specificity and inter-rater reliability as well as ease of use in clinical practice.

**Conclusion:** In the modern day diagnosis of AMI, the Sgarbossa criteria remain a valid and necessary tool in daily clinical practice. Recognition of the criteria initiates the algorithm for reperfusion therapy, dictates total coronary occlusion time, and directly affects patient outcomes. In this gentleman, an immediate diagnosis of a ST-elevation myocardial infarction activated the cardiac catheterization team. He was taken within 90 minutes for coronary angiography and primary percutaneous revascularization of a 90% mid left anterior descending coronary artery stenosis. Transthoracic echocardiography performed 24-hours after presentation documented a left ventricle ejection fraction of 35% with anterior and apical akinesis. The patient was managed according to contemporary guidelines and was referred to a cardiac rehabilitation program upon discharge.
EP-CLIN-2

EFFECTS OF THERAPEUTIC HYPOTHERMIA FOR CARDIAC ARREST: A SYSTEMATIC REVIEW

Meagan Dunn, Yazid Al Hamarneh, Ben Vandermeer, Patricia Chatterley Mlis, Ross T. Tsuyuki

Background: Therapeutic Hypothermia (TH) is a commonly applied therapy following resuscitation from cardiac arrest. The intent of the therapy is to mitigate neurological damage that results from ischemia that occurs during the cardiac arrest, as well as to improve survival. The effects of TH on neurological outcomes is not well documented. As such, we conducted a systematic review of TH on neurological outcomes in patients resuscitated from cardiac arrest.

Methods: We systematically searched for all studies to March 16, 2015 that looked at adult patients resuscitated from cardiac arrest who subsequently received TH for ≥ 12 hours, as compared with a control group that did not receive TH. The outcome of interest was neurological outcome and survival.

Results: We initially retrieved 1749 titles, and included 40 studies (17,627 patients) in our review. We found that TH was associated with more favourable neurological outcomes: RR 1.75 (95% CI 1.54, 1.99; p<0.001). In the 37 studies that reported on survival, the benefit of TH on survival was significant: RR 1.48 (95% CI 1.33, 1.65; p<0.001).

Conclusion: This systematic review supports the use of TH in the treatment of patients resuscitated from cardiac arrest. We identified a need for more studies that are prospective in design, with longer follow-up periods and systematic evaluation of neurological outcomes.
CLINICAL RELEVANCE OF THE FIRST AVAILABLE 12 LEAD ECG IN PATIENTS WITH SYMPTOMS SUSPICIOUS FOR ACUTE CV DISEASE: PROVIDING RAPID OUT OF HOSPITAL ACUTE CARDIOVASCULAR TREATMENT-3 (PROACT-3) ECG SUBSTUDY

Rabia Kashur, Y Zheng, S Sharma, D Weiss, W Tymchak, M Chan, J Ezekowitz, Robert Welsh

Background: From ECG Core Laboratory analysis in the PROACT-3 study in pre-hospital patients with symptoms suspicious for acute cardiovascular disease; we have demonstrated dynamic ECG changes in the majority of patients regardless of their final clinical diagnoses. To address the relevance of these findings we applied a practical approach using clinically relevant ST segment change to assess correlation to: adjudicated diagnoses, peak biomarkers, patient disposition and 30 day death/readmission.

Methods: PROACT-3 enrolled pre-hospital patients with acute chest discomfort or dyspnea. We analysed subjects with first available ECGs in a core ECG laboratory. Subjects were categorised according to adjudicated diagnoses into four groups: Cardiac including (ACS, AHF and angina), other cardiovascular diagnoses (CV), Chest pain not yet diagnosed (CPNYD) and Non-Cardiac. Magnitude of ST deviation was categorised into normal or abnormal with ST deviation in 2 contiguous leads of: 0.5-1mm, 1.5mm to 2mm and ≥ 2.5mm.

Results: Total of 422 subjects with analysed ECGs had the following adjudicated diagnoses: Cardiac 104 (24.6%), Other-CV 32(7.6%), CPNYD 189(44.8) and Non-Cardiac 97(23.0%). 242 subjects had normal ECGs while 180 were abnormal. Those with abnormal ECGs had higher rates of Cardiac and other CV diagnoses than those with normal ECGs (P=0.004). CPNYD and Non-cardiac diagnoses also observed less in those subjects with abnormal ECGs than normal ECGs (P=0.004). Subjects with abnormal ECGs had higher peak BNP levels (P <0.001) and higher rates of peak BNPs ≥400 (P <0.001). In addition, they had lower rates of discharge P=0.002 and higher rates of receiving (PCI) (P=0.004). Among those with abnormal ECGs, the proportion of subjects with Cardiac and other CV diagnoses increased as the magnitude of ST deviation increased while CPNYD and Non-cardiac diagnoses decreased. Similarly the rates of discharge from ED decreased (P=0.037) as the magnitude of ST deviation increased. Peak troponin levels positively correlated to the extent of ST deviation (P=0.001).

Conclusion: In Pre-hospital patients with suspected cardiovascular symptoms, the magnitude of ST deviation is directly related to the proportion of number of cardiac diagnoses, peak cardiac biomarkers and need for hospital admissions.
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<th>Normal ECG</th>
<th>Abnormal ECG</th>
<th>P</th>
<th>Abnormal</th>
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<td>0.5-1 mm</td>
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<td>n</td>
<td>242</td>
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<td><strong>Adjudicated diagnosis</strong></td>
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<td>Cardiac</td>
<td>49 (20.2)</td>
<td>55 (30.6)</td>
<td>0.004</td>
<td>20 (28.6)</td>
<td>18 (24.0)</td>
<td>17 (48.6)</td>
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<td>13 (5.4)</td>
<td>19 (10.6)</td>
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<td>4 (5.7)</td>
<td>10 (13.3)</td>
<td>5 (14.3)</td>
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<td>CPNYD</td>
<td>124 (51.2)</td>
<td>65 (36.1)</td>
<td></td>
<td>34 (48.6)</td>
<td>22 (29.3)</td>
<td>9 (25.7)</td>
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<td>Non Cardiac</td>
<td>56 (23.1)</td>
<td>41 (22.8)</td>
<td></td>
<td>12 (17.1)</td>
<td>25 (33.3)</td>
<td>4 (11.4)</td>
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<td>Peak BNP (pre/in hospital)</td>
<td>50.0 (12.0, 119.0)</td>
<td>113.5 (26.0, 392.0)</td>
<td>&lt;0.001</td>
<td>45.0 (12.0, 218.0)</td>
<td>199.5 (79.5, 530.5)</td>
<td>133.0 (78.0, 567.0)</td>
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<td>Peak BNP &gt;=400</td>
<td>10 (7.8)</td>
<td>25 (24.5)</td>
<td>&lt;0.001</td>
<td>8 (17.0)</td>
<td>12 (30.0)</td>
<td>5 (33.3)</td>
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<td>Peak trop (pre/in hospital)</td>
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<td>0.1 (0.0, 0.2)</td>
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<td>0.1 (0.0, 0.1)</td>
<td>0.1 (0.0, 0.1)</td>
<td>0.5 (0.1, 4.4)</td>
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<td>Peak trop &gt;=0.03</td>
<td>121 (71.2)</td>
<td>93 (71.0)</td>
<td>0.972</td>
<td>33 (62.3)</td>
<td>39 (73.6)</td>
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<td>Discharged from ED</td>
<td>185 (76.4)</td>
<td>113 (62.8)</td>
<td>0.002</td>
<td>50 (71.4)</td>
<td>47 (62.7)</td>
<td>16 (45.7)</td>
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<td>30-d Death,</td>
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<td>4 (2.2)</td>
<td>0.435</td>
<td>1 (1.4)</td>
<td>2 (2.7)</td>
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<td>37 (20.6)</td>
<td>0.464</td>
<td>9 (12.9)</td>
<td>17 (22.7)</td>
<td>11 (31.4)</td>
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<td>13 (7.2)</td>
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<td>5 (14.3)</td>
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AN INTERESTING CASE OF HEART BLOCK – LYME CARDITIS

Brent M. McGrath, Xi Zhao

Background: Lyme disease is the most common tick-borne infection in the northern hemisphere. It is a multisystemic condition caused by the spirochete Borrelia burgdorferi. In the United States, it is endemic in the Northeastern and Middle Atlantic regions, as well as the upper Midwest and northern Pacific Coast. The clinical course of Lyme disease is typically divided into three stages: early localized, early disseminated and late disease. The early disseminated stage occurs weeks to months after the rash first appears and is the stage during which cardiac symptoms often manifest. The diagnosis is suspected based on the clinical presentation, supported by positive serology on enzyme-linked immunoabsorbent assay and confirmed though a Western blot analysis.

Methods: A 37-year-old male presents to his local emergency department with three days of progressive shortness of breath. On the day he presented he reported an inability to get out of bed without feeling short of breath. He also reported concurrent near syncope upon standing. He had no similar episodes previous to this. His past medical history was significant only for regular cigar smoking. He was on no regular medications, and denied any excess alcohol or illicit drug use. The ECG reveals third degree atrioventricular (AV) block with an underlying non-conducting sinus rhythm at a rate of about 80 beats/min and a ventricular escape rhythm at a rate of 30 beats/min.

Results: In our patient, it was subsequently discovered that he had recently been bitten by a tick at his primary residence in the Northeastern United States. The infectious disease service was consulted and the patient was tested for Borrelia burgdorferi infection. Initial serology was positive for Lyme disease. Cardiac magnetic resonance imaging revealed a small area of gadolinium enhancement in the basal septum further supporting the diagnosis. As a result, the patient was started empirically on intravenous ceftriaxone for presumed Lyme carditis. Subsequent Western blot testing confirmed the diagnosis.

Conclusion: Approximately 4–10% of patients with Lyme disease have cardiac involvement on initial presentation. Cardiac manifestations typically occur during the early disseminated phase of the illness with transient AV block being the most common manifestation. Electrophysiological studies suggest that the heart block usually occurs above the bundle of His, typically within the AV node. Patients with first-degree AV block and a PR interval less than 300 ms are low risk and can be treated as an outpatient. For patients presenting in first-degree AV block with a PR interval greater than 300 ms, or those with higher degrees of AV block, inpatient treatment with parenteral ceftriaxone is recommended. Most cases of Lyme carditis resolve in one to two weeks with antibiotics and do not require insertion of a permanent pacemaker. Our patient was managed expectantly and no temporary venous pacing was required. Over several days, his conduction abnormality began to improve initially evidenced by a narrowing of his QRS complex followed by improvement in AV nodal conduction from third-degree to first-degree heart block. He was discharged in stable condition.
INCIDENCE, TREND AND MORTALITY OF VENOUS THROMBOEMBOLISM: THE AB-VTE STUDY

Ghazi S. Alotaibi, Cynthia Wu, Ambikaipakan Senthilselvan, Michael Sean McMurtry

BACKGROUND: The burden of venous thromboembolic disease (VTE) is major and comprehensive epidemiological studies profiling the epidemiology and patterns of health services use are needed. In this study we provided contemporary estimates of VTE incidence, case fatality and described the incidence trend over the last decade.

METHODS: This is a population-based data developed by linking 6 administrative health databases in Alberta (Canada) from April 1, 2002 to March 31, 2012. We defined acute symptomatic cases using a validated algorithm and used Poisson regression to model annual VTE counts.

RESULTS: We identified 31656 cases of acute symptomatic VTE. The age and sex-adjusted incidence rate of VTE was 1.38 (95% CI: 1.37, 1.40) per 1000 person-years. For pulmonary embolism (PE) it was 0.38 (95% CI: 0.36, 0.40) and for deep vein thrombosis (DVT) it was 1.0 (95% CI: 0.99, 1.1). The adjusted model showed no significant change in the incidence of VTE during the study period. The 30-day case fatality rate of VTE was 2.0% (95% CI: 1.89, 2.21). In patients with PE, the cases fatality was doubled at 30-day to 3.9% (95% CI: 3.50, 4.33). The 1-year case fatality was 9.2% (95% CI: 8.88, 9.52) for VTE and 12.9% (95% CI: 12.2, 13.6) in patients with PE. The case fatality rate increases with age in all VTE types.

CONCLUSION: The proportion of patients with community-acquired first-time venous thromboembolism has remained relatively unchanged during the study period. Further work to identify and provide prophylaxis to high-risk patients is needed.
EPI-CLIN-2

PULMONARY VEIN STENOSIS OF PREMATURITY: EPIDEMIOLOGY AND SURVIVAL FROM A MULTICENTER COHORT

Linda Mahgoub, Tarek Kaddoura, Ashok Kakadekar, Frank Dicke, Paloma Lopez Ortego, Rebecca Kameny, Maria Jesus Del Cerro, Jeff Fineman, Andrew Redington, Ian Adatia

Background: Premature birth may be associated with PVS.

Methods: We undertook a retrospective multi-center cohort study of patients born prematurely and diagnosed with PVS between 2000-2014. We excluded total anomalous pulmonary venous drainage, heterotaxy or gestational age ≥37wks.

Results: We identified 39 patients, 67% were male, median gestational age was 28-weeks (22wks-36wks) and mean birth weight was 1.1kg (433g-2645g). 15 patients (38%) were one of twins whose twin-siblings were unaffected. At diagnosis 72% had developed chronic lung disease (CLD) and 51% were discharged on home oxygen. History of PDA ligation was present in 31% of patients and necrotizing enterocolitis in 23%. 82% of patients underwent echocardiography in the neonatal period without diagnosis of PVS. Median age at PVS diagnosis was 6.5 months (1m-6yrs). Evaluation for pulmonary hypertension in 67% of patients led to a diagnosis of PVS. In 23% of patients PVS was found incidentally. PVS was diagnosed by echocardiography in 56% of patients and contrast CT-angiography, MRI or cardiac catheterization in 44%. Unilateral PVS was found in 64% of patients and 88% of these had a left-side involvement. Management included surgery in 46 %, supportive therapies in 44 % and a palliative approach in 10%. Freedom from death or re-stenosis for all patients was 73% at 1-year and 55% at 2, 5,10 years. PVS diagnosed before 6 months was associated with shorter survival.

Conclusion: PVS in infants who were born prematurely may be unapparent at birth, associated with pulmonary hypertension, CLD and O2 dependency and is often overlooked by routine echocardiogram. There is a male predisposition and predilection for left sided veins. The occurrence of PVS in one twin suggests that epigenetic factors may be important in the postnatal development or worsening of PVS.
COMPLETE VERSUS CULPRIT-ONLY PCI FOR STEMI WITH MULTI-VESSEL CORONARY ARTERY DISEASE: AN UPDATED META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Seraj Abualnaja, Mohammed Almutawa, Jay Shavadia, Robert C. Welsh, Kevin R. Bainey

Background: Patients with ST-elevation myocardial infarction (STEMI) are most commonly treated with culprit-only percutaneous coronary intervention (PCI). However, recent randomized trials suggest benefit with complete revascularization. We performed an updated meta-analysis comparing routine culprit-only PCI versus multi-vessel PCI in STEMI.

Methods: MEDLINE, EMBASE, ISI Web of Science and CENTRAL were searched from 1996 to April 2015. Relevant conference abstracts were searched from January 2002 to April 2015. Studies included STEMI with multi-vessel disease receiving primary PCI. The primary endpoint was long-term death and/or myocardial infarction (MI). Data were combined using a random-effects model.

Results: 6 randomized trials (1790 patients, 959 multi-vessel PCI and 831 culprit only PCI) were included. There was no significant difference in death or death/MI with multi-vessel PCI versus culprit-only PCI (OR 0.74, 95% CI 0.44-1.25, p=0.26; OR 0.64, 95% CI 0.31-1.40, p=0.27, respectively). However, repeat revascularization was reduced with multi-vessel PCI (OR 0.36; 95% CI 0.25-0.52, p<0.0001).

Conclusions: In patients with STEMI and multi-vessel disease, our analysis found no significant reduction in death and/or myocardial infarction long-term. The results of this study support the continuation of the COMPLETE trial.
Background: ST elevation myocardial infarction (STEMI) requires urgent and timely medical attention. Limiting reperfusion delay is crucial to management and health care outcomes. Patients’ education, awareness of these symptoms and utilization of medical resources can vary among different cultures. We aim to explore those differences between patients in Canada and the Kingdom of Saudi Arabia (KSA).

Methods/Results: A standard questionnaire designed to assess knowledge, behaviors and factors related to seeking medical attention was used. The questionnaire was administered post STEMI in conjunction with the Canadian ‘Which Early ST-Elevation Therapy’ study and subsequently post STEMI in KSA. The sample included a total of 211 participants, 111 Canadian patients and 100 KSA patients. The symptom onset occurred at home in 62.4% of Canadians and 76% of KSA STEMI patients. More than two-thirds of the KSA patients tried a conservative method such as relaxing or praying as the first response to symptoms compared to approximately one-third of Canadians (65% vs 38.6%) with patients first action shown in figure. The onset of symptoms was at rest in 49.1% Canadians vs. 66% of KSA and during active exertion in 50.9% vs. 34% respectively. Chest discomfort/pain at presentation was described in 21.6% of Canadians 28.5% of KSA and was described as severe (≥7/10) in 73% and 61% respectively. Regarding first medical contact, Canadians activated the pre-hospital EMS ambulance system 74% of the time compared to only 4% in KSA. Of those Canadian STEMI not activating EMS: 45% stated it was easier to drive and 27% quoted cost concerns. In KSA STEMI patients: 62% stated they did not think of an ambulance and 20% stated it would be easier to drive. The majority of Canadians were prompted about the possible cardiac nature of their symptoms early on by a family member vs. only 16 % in KSA. The educational background varied widely between the two groups, with 45% of Canadians carrying a higher education from a university or college vs. only 7% in KSA.

Conclusions: This cross-sectional study demonstrates some similarities in the clinical presentation of ACS between the two groups. However, a difference exists in health care seeking behaviors among participants. These findings may be related to differences in health literacy, cultural factors, or the structure of the health care system. Further research to identify the underlying factors is needed to guide the need for interventions to improve rapid identification of ACS symptoms and health care access.
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IHD-CLIN-3

QUALITY OF LIFE IN DIABETICS WITH MULTI-VESEL CORONARY DISEASE: REAL-WORLD EXPERIENCE COMPARING PERCUTANEOUS CORONARY INTERVENTION AND CORONARY ARTERY BYPASS GRAFTING SURGERY

Brent M. McGrath, Colleen M. Norris, Kevin Bainey

Background: Studies have consistently demonstrated a mortality benefit supporting coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in the revascularization of diabetic patients with multi-vessel coronary artery disease. In spite of advances in medical therapy and the advent of drug-eluting stents, CABG has still maintained superiority over PCI with regards to long-term clinical outcomes. However, CABG in the short term is associated with higher peri-operative mortality and longer recovery time with higher rates of peri-operative stroke. This suggests that while CABG may prolong life, it’s impact on patients quality of life warrants further study. Recent data from the FREEDOM Trial suggests that CABG may be superior to PCI in terms of its impact on patient quality of life at 2 years; however, the difference was small and this study population may not reflect real-world experience. Accordingly, our aim is to compare the effects of each revascularization technique on quality of life (QOL) in diabetics with multi-vessel CAD over the long-term.

Methods: The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) is an outcomes initiative capturing all patients undergoing cardiac revascularization in Alberta, Canada that commenced in 1995. Like in FREEDOM, health status in the APPROACH database is measured using the well-validated Seattle Angina Questionnaire (SAQ). The SAQ is a 19-item self-administered disease-specific questionnaire measuring five domains of health status: anginal stability, anginal frequency, exertional capacity, quality of life and treatment satisfaction on a Likert-type scale (lower score equate to worse outcomes). Using APPROACH, we identified 1319 diabetic patients with multi-vessel CAD requiring revascularization from January 2009 to December 2012 who reported health status outcomes using the SAQ at baseline, 1 and 5 years (599 CABG; 720 PCI). Adjusted analysis was performed using a propensity score-matching technique.

Results: At baseline, adjusted mean scores were lower with CABG compared to PCI: exertional capacity (64.5 vs. 74.4, p<0.001), angina frequency (75.7 vs. 85.2, p=0.001), treatment satisfaction (85.5 vs. 89.5, p=0.018), quality of life (59.6 vs. 70.0, p<0.001). However, at 1-year improved adjusted mean scores were noted in favor of CABG: exertional capacity (80.5 vs. 79.5, p=0.54), angina frequency (81.7 vs. 77.1, p=0.001), treatment satisfaction (93.2 vs. 92.1, p=0.004), quality of life (81.7 vs. 77.1, p=0.002). However, at 5-years, results were attenuated: exertional capacity (77.6 vs. 78.7, p=0.60), angina stability (77.8 vs. 74.8, p=0.19), angina frequency (94.0 vs. 91.7, p=0.08), treatment satisfaction (94.1 vs. 92.8, p=0.22), quality of life (84.2 vs. 82.2, p<0.21).

Conclusion: Taking into consideration worse baseline status, CABG compared to PCI in diabetics with multi-vessel CAD still improved 1-year health-related quality of life. However, these outcomes were not sustained at 5-years. Our findings should be taken into consideration when contemplating a revascularization strategy in diabetics with multi-vessel CAD.
TIME IS MUSCLE – THE IMPORTANCE OF EARLY ECG RECOGNITION AND PROMPT CLINICAL ACTION

Brent M. McGrath, Inka Toman

Background: Hyperacute T-waves refer to positive-deflection, tall-amplitude, primary T-wave abnormalities associated with acute myocardial infarction (MI). A T-wave amplitude that is less than two-thirds of the R-wave amplitude is generally accepted as normal. More specifically, the T-waves should be less than 0.5 mV in the limb leads and 1.5 mV in the precordial leads. The modern classification of MI makes a distinction between those with ST-segment elevation (representing transmural infarction) and those without, with important resultant treatment and prognostic significance. In the setting of acute STEMI, hyperacute T-waves are often the first ECG sign of complete coronary artery occlusion, typically developing within minutes of symptom onset. Moreover, in 2-8% of patients with a transmural anterior MI, hyperacute T-waves persist without the evolution of STE. This makes prompt recognition of this ECG manifestation of ischemia important.

Methods: A 46-year-old male presents to the University Hospital emergency department with acute-onset retrosternal chest pain. The patient described this pain as feeling like a “rock” on his chest. He indicated that the pain developed suddenly while he was at rest 90 minutes before presenting to hospital and radiated to his left arm. He also reported associated near syncope and diaphoresis. He had no similar episodes previous to this. His past medical history was significant only for regular smoking and a 20 pack-year history. He was on no regular medications, and denied any excess alcohol or illicit drug use. His blood pressure was 107/66 and equal bilaterally. The initial ECG revealed sinus bradycardia at a rate of 57 beats/min with prominent anterior T-waves and ST-depression in limb leads III and aVF. There was no prior ECG for comparison.

Results: Given the clinical history, the ECG findings were interpreted to represent an acute MI with hyperacute T-waves in the anterior leads and resultant reciprocal ST-depression in the inferior leads. The patient was initiated on dual antiplatelet therapy and anticoagulation in accordance with contemporary acute coronary syndrome guidelines while arrangements were made for urgent cardiac angiography. On angiography, the patient was found to have a 100% occluded proximal left anterior descending (LAD) artery to which a drug eluting stent was deployed. Subsequent echocardiography revealed a near-normal left ventricular ejection fraction of 50-55%.
Conclusion: Hyperacute T-waves have been found to be associated with complete occlusion of the proximal LAD. Recent evidence from cardiac magnetic resonance imaging studies suggest that patients presenting with hyperacute T-waves show the typical transmural necrosis seen in STEMI patients, making prompt recognition, diagnosis and intervention important. The differential diagnosis for prominent T-waves commonly includes acute MI, hyperkalemia, left ventricular hypertrophy and benign early repolarization. The term hyperacute specifically refers to the T-wave associated with acute MI. This T-wave is often symmetric and broad-based. Importantly, it may be associated with ST depression in reciprocal ECG leads, which aids in diagnosis. If the ECG changes and clinical context suggest acute MI, prompt treatment with invasive coronary revascularization may be warranted. The patient was discharged home in stable condition.
MEDBIKE: A TECHNOLOGICAL SOLUTION FOR POOR PATIENT PARTICIPATION IN CARDIAC REHABILITATION

Peter W Wood, Ga Young Kim, Stephanie Sheaffer, Kenton Hamaluik, Pierre Boulanger, Robert Haennel

Background: Regular exercise improves morbidity and mortality in the majority of cardiac patients. This is the basis for which cardiac rehabilitation (CR) is utilized. Reportedly all-cause and cardiac mortality, and non-fatal myocardial reinfarction decreases by 20 to 25% over a 3 year period with exercise intervention. Furthermore, non-participants or drop-outs from exercise programs have been reported to have a 30% lower survival rate than those who participate. Even though this is the case, therapeutic cardiac rehabilitation (CR) is severely underutilized. A novel prototype CR system (MedBIKE) has been designed in the Advanced Man Machine Interface (AMMI) laboratory, University of Alberta, which will improve: 1. the compliance of rehab patients to their physical activity programs; and 2. long term adherence of patients to more active lifestyles, relative to the physical activity (PA) habits they exhibited prior to their cardiac event.

Methods: We would like to perform a pilot study to demonstrate the MedBIKE system’s ability to improve patient compliance to CR exercise programs, and adherence to long term PA adoption. A prototype system has been developed out of the AMMI laboratory. This system provides a virtual world for a patient to cycle through on a standard mountain bike while having a video-audio feed and their bio data (ECG, blood pressure and oxygen saturation) recorded and transmitted in real-time to a clinician located at a remote site. A total of 36 low risk, disease matched patients will be enrolled into this randomized control trial which will include 18 patients per arm (intervention and control). The intervention arm will carry out standardized CR PA programs using the MedBIKE from a remote location (Edmonton City Commonwealth Community Recreation Center), instead of at the CR facility (Jim Pattison Centre for Heart Health). It is the vision of this project that following this pilot study, on low risk cardiac patients, a larger follow-up study is performed on higher risk patients (i.e. large territory myocardial infarcts and heart failure patients) and the system is moved into the home. This will demonstrate the versatility of the MedBIKE system and inform as to whether most CR patients can be exercised under remote supervision, with the goal of vastly improving the overall CR exercise program compliance level.

Results: Data recording and analysis will occur at two stages in this study: 1. following the 8 week clinical rehabilitation phase, and 2. 12 weeks following the end of the clinical phase; both to be carried out at the Commonwealth Centre. Subjects will be assessed at the end of the 8 week program and 12 week post clinical phase, to assess whether they are still performing regular exercise sessions. If not, specific reasons for lack of compliance and adherence will be determined. To minimize bias, the interviewer will not know which arm of the study the subject has been randomized to.

Conclusion: The MedBIKE is a technological solution for improving CR patient compliance to PA programs and improving long term CR adherence to positive lifestyle modifications.
COMPARISON OF THE ALIGNMENT OF SITE VERSUS ADJUDICATION COMMITTEE-BASED DIAGNOSES WITH THE PATIENTS’ OUTCOME: LESSONS LEARNED FROM PROACT-3 TRIAL


Background: Within clinical trials, adjudication by a central adjudication committee (CAC) plays an important role in the assessment of outcomes. Controversy exists regarding the utility of CAC versus site-based assessments and their relationship to subsequent clinical events.

Methods: This study is a secondary analysis of the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial, which randomized patients with chest pain or shortness of breath for biomarker testing in the ambulance. The ED physician diagnosis was recorded, and an adjudicated diagnosis was assigned by the CAC using formal guidelines. The level of agreement between ED and CAC diagnosis was evaluated using Kappa coefficient, and compared to clinical outcomes (30-day re-hospitalization, 30-day and 1-year mortality).

Results: Of 477 patients in PROACT-3, 49.3% were male, median age was 70 years, and hospital admission rate was 31.2%. The ED physicians and the CAC disagreed in 55 cases (11.53%) resulting in a kappa= 0.71 (95%CI: 0.64-0.78). The 30-day re-hospitalization, 30-day mortality and 1-year mortality was 22%, 1.89% and 9.43% respectively. Although there were similar rates of re-hospitalization irrespective of adjudication, in cases of disagreement compared to agreement between CAC and ED diagnosis, there was a higher 30-day (7.27% vs. 1.18%, p=0.002) and 1-year mortality (27.27% vs. 7.10%, p<0.001).

Conclusion: Despite the substantial agreement between the diagnosis of ED physicians and CAC, in those patients where there was disagreement, there was a worse short-term and long-term mortality.
YOUNG WOMEN POST-MI HAVE HIGHER PLASMA CONCENTRATIONS OF INTERLEUKIN-6 BEFORE AND AFTER STRESS TESTING

Cherie R. Rooks, Ijeoma Ibeanu, Amit Shah, Pratik Pimple, Nancy Murrah, Lucy Shallenberger, Thaddeus Pace, J. Douglas Bremner, Viola Vaccarino, Paolo Raggi

Objectives: Young women have poorer prognosis after myocardial infarction (MI) and a higher rate of mental stress-induced ischemia compared with similarly aged men. A higher inflammatory status may help explain these sex differences.

Methods: We examined 98 patients (49 women and 49 men) age 18-59 years with recent MI (past 6 months). Women and men were matched for age, type of MI, and time since MI. Interleukin 6 (IL-6) concentrations were measured at baseline, after mental stress using a speech task, and after exercise/pharmacologic stress (60 and 90 min). Depressive symptoms were measured with the Beck Depression Inventory (BDI-II) and angiographic coronary artery disease (CAD) severity was quantified with the Gensini score. Single-photon emission computed tomography (SPECT) was used to obtain a computerized measurement of stress-induced ischemia (summed difference score, or SDS) and determine whether severity of stress-induced ischemia affects the inflammatory response to stress. Analysis was stratified by the median age of 50. Geometric mean concentrations of IL-6 were obtained from general linear regression models.

Results. In both age groups, women had less angiographic CAD and a similar level of conventional risk factors compared with men. Despite this, baseline IL-6 geometric means before both mental and physical stress were twice as high in women ≤50 years of age compared to age-matched men (3.8 vs. 1.8 pg/mL, p=0.001, across both conditions), while they were similar in women and men age >50 years (2.3 vs. 2.2 pg/mL, p=0.83). After mental stress, IL-6 concentrations increased in both women and men in a similar fashion and remained twice as high in women ≤ 50 years than men at both 60 min (5.4 vs. 2.6 pg/mL, p=0.002) and 90 min (5.9 vs. 3.4 pg/mL, p=0.01). No significant difference was found between women and men >50 years of age at any time point after mental stress. Results were similar for physical stress. After accounting for SDS, IL-6 concentrations in young women remained higher after both mental and physical stress. Baseline IL-6 concentrations were not significantly related to inducible ischemia.

Conclusions: After MI, young women aged 50 years or younger, compared with age-matched men, have remarkably higher concentrations of inflammation at baseline and after both mental and physical stress, with a similar inflammatory response to both stressors. Sustained concentrations of inflammation in young women, not their response to stress, may contribute to their adverse outcomes post-MI.
TELOMERE LENGTH AND CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS

Michelle J. Ormseth, Joseph F Solus, Annette M Oeser, Aihua Bian, Tebeb Gebretsadik, Ayumi Shintani, C Michael Stein, Paolo Raggi

Background/Purpose: Telomeres protect against DNA damage and shorten with each cell division; their length may be a marker of cardiovascular and overall biological aging. Patients with rheumatoid arthritis (RA) have accelerated cardiovascular disease resulting in early mortality. The relationship between telomere length and atherosclerosis in RA is not known. We examined the hypothesis that reduced telomere length is associated with increased coronary atherosclerosis in RA.

Methods: We performed a cross-sectional study in 145 patients with RA and 87 control subjects matched for age, race and sex. Coronary artery calcium score, a measure of coronary atherosclerosis, was determined by non-contrast cardiac computed tomography. Telomere length was measured from DNA extracted from whole blood, using real-time quantitative polymerase chain reaction and expressed as the ratio of telomeric repeats to a single-copy gene (T/S ratio). The associations between telomere length and coronary artery calcium score and disease activity (DAS28) were assessed with Spearman correlation, proportional odds logistic regression, and linear regression adjusting for age, race and sex in patients with RA.

Results: Telomere length was significantly inversely associated with age in patients with RA (rho=-0.37, P<0.001) and control subjects (rho=-0.39, P=0.001). Among patients with RA, for every interquartile range (IQR) decrease in telomere length (T/S ratio), the odds of higher coronary artery calcium score increased by 38% (95% CI: 4, 60%), after adjusting for age, race and sex (P adjusted= 0.03). Telomere length was not associated with DAS28 (P adjusted= 0.17). Telomere length was not significantly different in patients with RA (median [IQR]: 1.02 units [0.9, 1.11 units]) compared to control subjects (1.05 units [0.95, 1.17 units]; P= 0.10).

Conclusion: Telomere length is inversely associated with coronary artery calcium score independent of age, race and sex in patients with RA.
VALUE OF CARDIAC MRI AND $^{18}$F-FDG PET-CT IN THE DIAGNOSIS OF CARDIAC SARCOIDOSIS

Richard Coulden, Emer Sonnex, Indrajeet Das, Hefin Jones, Jonathan Abele

**Background:** Sarcoidosis is a multisystem disorder with cardiac involvement in 25% of cases\(^1\). Diagnosis of cardiac involvement is challenging with FDG-PET and cardiac MRI (CMRI) proving most reliable. We compare FDG-PET and CMRI with late gadolinium enhancement (LGE) in patients with suspected cardiac sarcoidosis and biopsy proven extra-cardiac disease.

**Methods:** 34 patients were investigated with FDG-PET CT and CMRI within 2 months (28 on same day). Patients undergoing FDG-PET followed a 24hr low-carbohydrate diet and overnight fast\(^2\). CMRI included T2-weighted STIR and PSIR-LGE 10 mins post 0.2mmol/kg GdDTPA. Images were reviewed by experienced readers blinded to the results of the other examination. FDG-PET was considered positive if any segment had SUVmax > 2.5; CMRI was considered positive if any segment showed ‘sarcoid-type’ LGE. In no case was edema present on STIR imaging without LGE in the same segment on PSIR.

**Results:** See image. 4 patients meeting Japanese criteria\(^3\) had no lung or node FDG uptake; 2 had intense generalized cardiac FDG uptake (SUVmax >5.0) and no LGE (likely diet non-compliant) and 1 had LGE but no myocardial FDG uptake (? old myocarditis versus cardiac sarcoidosis). 1 had no lung or node FDG uptake and no LGE or cardiac FDG uptake, presumed no metabolically active disease or scar. 10 patients had biopsy proven extra-cardiac disease but did not meet Japanese criteria. None of these had myocardial FDG uptake or LGE.

**Conclusions:** The combination of FDG PET and LGE CMRI has advantages over either technique alone. Cardiac FDG uptake without FDG avid disease in lung or nodes may be due to diet non-compliance. Cardiac LGE is non-specific and, without evidence of FDG avid disease elsewhere, may represent non-active fibrotic sarcoidosis. This study shows the potential for combining FDG PET and CMRI in suspected cardiac sarcoidosis and other inflammatory cardiac conditions.
Sarcoidosis is a multisystem disorder with cardiac involvement in 25% of cases (1). FDG-PET and cardiac MRI (CMRI) have been used for diagnosis but their individual and combined roles in monitoring disease activity and response to treatment is unclear. We describe 9 patients with suspected cardiac sarcoidosis who underwent repeat FDG-PET/CMRI 5-10 months apart during monitoring.

FDG-PET CT and CMRI were performed within 48 hours of each other. Patients undergoing FDG-PET followed a 24 hour low-carbohydrate diet and overnight fast (1). CMRI included short axis cine assessment of left ventricular (LV) function and PSIR-late gadolinium enhancement (LGE) 10 minutes post 0.2mmol/kg GdDTPA. Images were reviewed by experienced readers blinded to the results of the other examination. FDG-PET was considered positive in mediastinal nodes, lung or myocardium if an area had SUVmax>2.5 or SUVmax 1.5>background bloodpool activity; CMRI was considered positive if any segment showed ‘sarcoid-type’ LGE.

See image 1. 3 patients had immunosuppressive therapy throughout, 2 started therapy between visits, 1 stopped therapy between visits and 3 had no therapy. 8 patients showed myocardial FDG uptake on visit 1 with 5 of these showing LGE. LGE did not occur in isolation (no myocardial FDG uptake). In 6 patients, myocardial FDG uptake resolved between visits with LVEF improving (>5% change) in 3. No patient with LGE on the initial visit showed LGE resolution despite resolution of myocardial FDG uptake in 3. One patient (no myocardial FDG or LGE) showed improved function although this was associated with improved rate control in AF (unrelated to cardiac sarcoidosis?).

In this small series, both myocardial FDG PET and LGE identify cardiac sarcoidosis involvement but only myocardial FDG uptake showed resolution between visits. Once identified, LGE did not change although LV ejection fraction did improve in some cases. FDG presumably reflects disease activity while LGE represents myocardial scar, which may be new or old.
A SIMPLE METHOD TO ESTIMATE GLOBAL LONGITUDINAL STRAIN FROM BIPLANE CONTRAST ECHOCARDIOGRAPHY: COMPARISON WITH STANDARD GLS MEASUREMENTS

Faisal Alghamdi, S. Tilly, A. He, I. Hassan, E. Pituskin, I. Paterson, J. Choy, Harald Becher

**Background:** Global longitudinal strain GLS measurements heavily depend on the quality of the 2D echocardiographic images. This excludes a substantial number of patients from assessment of GLS. Contrast echocardiography has been shown to improve endocardial definition.

**Methods:** In 75 patients with good acoustic windows and no obvious foreshortening of the imaging planes, GLS measurements were performed according the ASE guidelines. In addition, simple contrast GLS (scGLS) was measured by manually tracing the end diastolic and end systolic endocardial contours of the 2D contrast echocardiographic loops similar to end diastolic and end systolic tracing for volume measurement but excluding the mitral ring diameter. This results in end diastolic and end systolic endocardial circumference (EDc, ESc). Peak systolic strain was calculated by (EDc-ESc)/EDc in each view and the average was reported as scGLS.

**Results:** Fig.1 shows the linear correlation between scGLS and GLS. Using Bland Altman plot there was a bias of 0.8% indicating only minor deviation of the scGLS measurements from the GLS measurements Fig.2.

**Conclusion:** GLS measurements using end systolic and end diastolic contrast echocardiographic frames (scGLS) showed good agreement with conventional GLS measurements. This will allow strain measurements in patients with poor acoustic windows when contrast agents are injected.
COST EFFECTIVENESS OF ROUTINE CONTRAST ECHOCARDIOGRAPHY TO RULE OUT LEFT VENTRICULAR THROMBUS IN ANTERIOR MYOCARDIAL INFARCTION

Jonathan Choy, Amr Hamour, Michelle Graham, Anthony Boardman, Harald Becher, Jonathan Choy

Background: Left ventricular (LV) thrombus formation is a well-recognized complication of anterior wall myocardial infarction (MI). Patients with documented LV clot have up to a 12% risk of embolization and stroke. While percutaneous coronary intervention (PCI) has been shown to decrease the incidence of infarct size, the need for dual anti-platelet therapy in combination with warfarin, results in a higher risk for bleeding complications. Current guidelines do not support routine oral anti-coagulation in addition to dual anti-platelet agents (triple therapy) unless clot is seen on echocardiography. Up to 15% of conventional echocardiograms are technically suboptimal, potentially under or over-diagnosing thrombus. Contrast echocardiography allows for higher diagnostic accuracy and optimal management of anti-coagulation in these patients. However many provinces, including Alberta do not have reimbursement for the cost of contrast, thereby limiting its use.

Methods: Based on Canadian Institute for Health Informatics data, ST elevation MI rates are estimated to be 0.8 per 1,000 population in Alberta. It is further assumed that 40% of these MIs are anterior in distribution with 85% undergoing PCI either as primary intervention or after successful reperfusion with thrombolysis. Rates of thrombus formation, embolization and reduction in stroke with appropriate anticoagulation were estimated using numbers derived from peer-reviewed published studies or meta-analyses. Costs for hospitalization due to strokes and major bleeds were derived similarly. The cost of one vial of contrast was taken to be $120. Contrast echocardiography was assumed to have a 95% sensitivity and specificity for detection of clot.

Results: It is estimated that 1,128 patients suffered from anterior MI in Alberta in 2014. Owing to higher detection rates of LV thrombus and appropriate anticoagulation, routine use of contrast echocardiography would reduce the absolute incidence of embolic stroke from 1.29% to 0.47%, resulting in a net gain of 47.49 quality adjusted life years (QALY). The higher use of triple therapy would however lead to a higher incidence of major bleeding in the contrast group (1.87% vs. 1.6%). Even accounting for costs of the contrast agent, the overall cost savings to the system would be $179,631.23, with an incremental cost effectiveness ratio of $2,849.78 per QALY gained. The break-even point for a vial of contrast for this indication is $279.

Cost comparison between conventional and contrast echocardiography

<table>
<thead>
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<th>Expenditures</th>
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<th>Contrast</th>
<th>Savings (costs)</th>
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<td>Total</td>
<td>$627,975.95</td>
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Conclusion: Routine contrast use to rule out LV thrombus after acute anterior MI is highly cost effective and should be considered for funding by the Alberta Government.
Background: Surgical repair of tetralogy of Fallot (TOF) often results in some degree of pulmonary valve incompetence or stenosis, leading to right ventricular dilation, hypertrophy, or a combination of the two. One of the major concerns for these patients then becomes their long-term ventricular myocardial mechanics. Although, focused analysis of this entity including longitudinal and circumferential strain can be done by echocardiography, this modality is often limited in adolescents and adults by poor acoustic windows. Given the growing trend of regular MRI screening for patients with prior TOF repair, it would be ideal to utilize this modality for myocardial deformation analysis. The aim of this preliminary study was to retrospectively describe the measurement of longitudinal and circumferential strain using routine cardiac MRI (CMR) sequences and novel software in repaired TOF compared to normal controls.

Methods: For this preliminary evaluation, 42 patients who had undergone TOF intervention were identified from the pediatric congenital CMR database and compared to 40 normal controls. Only the most recent study was included in the instances where serial examinations had been completed. Clinical and volumetric data was taken from the MRI report. Global right ventricular (RV) longitudinal strain was measured from the standard 4-chamber CINE steady state precession (FISP) sequence. Basal RV circumferential strain was measured from the standard short axis CINE FISP sequence just caudal to the RV outflow tract. Measurements were performed using a locally developed novel CMR software that utilizes a semi-automatic segmentation program similar to the well-known and commercially available feature-tracking software for measuring strain by CMR.

Results: 33/42 studies on patients with TOF met inclusion criteria. Data from 40 normal patients were analyzed as well. The mean age for TOF patients was 13.5 years old (1 year-20 years old) and was 11.6 years old (10 days-17 years old) for normal patients. The mean BSA for both TOF and normal patients was 1.40 m².
A GPU ACCELERATED REGISTRATION APPROACH WITH APPLICATION TO RV SEGMENTATION

Kumaradevan Punithakumar, Pierre Boulanger, Michelle Noga

Background: Image registration is the process of obtaining a mapping between a pair of images, an important component in many medical imaging applications. Image registration algorithms generally require many iteration loops, and are therefore computationally expensive. Traditional single Central Processing Unit (CPU) based implementations takes considerable amount of time to compute the registration, and therefore, limit the application for standard clinical applications. This study presents a Graphical Processing Unit (GPU) computing approach to accelerate the performance of a moving mesh based non-rigid registration algorithm. The moving mesh correspondence algorithm has been shown to be effective for automated delineation of the right ventricle (RV) from a sequence of cardiac magnetic resonance (MR) images [1]. In addition to GPU computing, the propose approach further parallelize the problem by image concatenation.

Method: Given the segmentation on the first frame, the proposed method segments both endocardial and epicardial borders of the RV using the obtained point. This allows us to analyse the cardiac function over the entire cardiac in addition to the computation of common clinical measures such as ejection fraction. The registration algorithm consists of transformation computation for each pixel in the moving image, calculation of similarity metric, and optimization. The proposed approach consists of two parallelization components: 1) implementation of parallel (Compute Unified Device Architecture) CUDA version of the registration algorithm; and 2) using image concatenation to further parallelize the moving mesh computation.

Results: The proposed method was evaluated over the Training data set provided by the MICCAI 2012 RV segmentation challenge, which contains short-axis MRI volumes of 16 subjects. The data was acquired on 1.5T MR scanners (Symphony Tim, Siemens Medical Systems, Erlangen, Germany) with steady-state free precession acquisition mode. We used a NVIDIA Tesla K40c to test the GPU version of the algorithm. The proposed method took an average of 4.36 seconds to segment a sequence of 19 MRI images, whereas the CPU version took 3991.7 seconds.

Conclusions: The proposed approach yielded a significant performance improvement over serial image registration approach. In the future, we plan to assess the applicability of the proposed algorithm over a large data set for cardiac functional analysis.

OBJECTIVES: Coronary artery calcification (CAC) is an important marker for future cardiac events and formal CAC scoring has been combined with myocardial perfusion imaging (MPI) for risk stratification. The utility of visual CAC scoring from low dose, non-gated CT (NGCT) obtained for attenuation correction has not been described. This study assesses the use of visual CAC score from attenuation correction NGCT in rubidium82 PET-CT (Rb-PET).

METHODS: 307 patient with suspected coronary artery disease (CAD) but no past history of CAD underwent Rb-PET with dipyridamole stress. Rest and stress NGCT were scored visually for CAC (scale 0 - 11) and Rb-PET was reported in the standard way (Corridor 4DM). A summed stress score (SSS) > 2 was considered positive for ischemia.
All patients were followed up by chart review at 6 months.

RESULTS: See table. Ischemia confirming events (ICE) are tabulated against CAC score ranges. 38 of 307 patients had an angiogram within 6 months. 14 of these were normal or showed non-obstructive disease (<70% stenosis in any vessel). Of those with ≥ 70% stenosis in one or more vessels, 4 went for CABG, 15 for PCI and 5 were treated medically. Only 1 of 24 ICE events occured in 163 patients with a CAC score 0-2, although 22 of these showed ischemia (SSS>2).

CONCLUSIONS: Patients with little or no coronary calcium (CAC score 0-2) and ischemia on Rb-PET (SSS>2) had virtually no events at 6 months. This study is small but suggests CAC score on attenuation correction NGCT is an important parameter and should be included as part of any Rb PET-CT report. – CIHR Research Support: Sub-study of Rb-ARMI registry (registry received CIHR funding).
CARDIAC MRI IN TURNER SYNDROME: IS IT JUSTIFIED IN CHILDREN?

Scott Somerville, Elizabeth Rosolowsky, Somjate Suntratonpipat, Benjamin H Goot, Rose Girgis, Edythe Tham

**Background:** Turner Syndrome (TS) patients may have congenital or acquired cardiac disease. Echocardiography (Echo) is currently the most commonly used modality to identify cardiac lesions, however, it may be insufficient to visualize the entire aorta in TS patients. The objective is to compare the ability of cardiac MRI and echo to detect cardiac lesions in patients with TS.

**Methods:** Prospective, cohort study of 19 TS patients, aged 8-18 years, presenting for routine follow-up at the Stollery Children's Hospital. Each patient had a cardiac MRI and echo within a year of each other. A cardiologist trained in both MRI and echo interpreted the results.

**Results:** 73.7% (14/19) of the TS patients had a cardiac lesion identified. Of those 14 patients with a cardiac lesion, 64.3% (9/14) had a discrepancy between echo and cardiac MRI. 77.8% (7/9) of the discrepancies were explained by a lesion found on cardiac MRI that was not visible on echo.

**Conclusion:** Cardiac MRI, which allows visualization of the entire aortic arch, identified clinically significant cardiac lesions that were missed by echo. While the implications are limited in children, these findings support the use of cardiac MRI to evaluate the aorta rather than by echo alone. Because of increased risk of aortic dissection in these patients, earlier identification of cardiac lesions, such as aortic dilation, will further understanding of the natural history of these lesions, and may identify which patients would benefit from early intervention.
WAVELET FUSION USING A LIKELIHOOD ESTIMATOR FOR 3D ECHOCARDIOGRAPHY

R.H. Abhilash, Kumaradevan Punithakumar, Alexander McNulty, Marina Biamonte, Michelle Noga, Pierre Boulanger, Harald Becher

Background: 3D echocardiography is seen as a promising modality for real-time imaging of the heart. A major bottleneck of 3DUS is the limited Field of View (FOV) due to which a single view might be insufficient to cover the whole geometry of the heart. In the past, image registration based approaches have been used to improve the FOV by fusing multiple views of the heart. However, they require large image overlap and are computationally intensive. Further their accuracy is bounded by image resolution. Ultrasound image fusion also poses the problem of minimizing speckle noise in the overlapping region while preserving useful features. The straightforward approach of averaging the images generally reduces the noise but tends decrease the contrast while maximum fusion increases the noise. This study presents a multi-camera based fusion technique that is independent of image quality and overlap. We propose a wavelet fusion technique for the overlapping region that uses a pixel-wise likelihood estimator which preserves useful features while reducing noise.

Methods: In the proposed multi camera approach, markers placed on the ultrasound probe are tracked in 3D space by a six-camera optical tracking system. In order to compensate for respiratory movement (which might otherwise lead to misalignment) the patient’s breathing pattern was tracked using abdominal markers. The ultrasound volumes of similar respiratory phase can now be aligned based on the spatial information provided by the optical tracking system. During fusion, the constituent images are decomposed into wavelet coefficients. We use a pixel-wise likelihood estimator based on the mean grayscale value and standard deviation in the neighborhood of the pixel. Individual components are weighted by the likelihood estimator values. The fused image is then obtained by taking an average of individual views and applying the inverse wavelet transform.

Results: The fusion technique was validated over ultrasound volumes obtained from 6 male subjects. The mean improvement in Field of View (FOV) was 34.46 ± 12.53%. We used four indices to quantitatively evaluate the image namely Contrast, Contrast to Noise Ratio (CNR), Signal to Noise Ratio (SNR) and Feature Count (FC). The indices were calculated over square patches in the myocardial and bloodpool regions in 242 image slices. The proposed wavelet based fusion showed improvements of 66.46 ± 21.68 (Contrast), 49.92 ± 28.71 (CNR), 57.59 ± 47.85(SNR) and 13.06 ±7.44 (FC) which was higher than the corresponding values for average and maximum fusion. We also conducted a qualitative study to assess the following clinically relevant parameters (in a scale of 5): i) clarity of myocardial border; ii) noise level; iii) visual contrast; iv) sharpness; and v) clarity of leaflet. The mean score for all indices was greater than 3 for the fused image which was higher than the corresponding values for individual views.

Conclusion: This study proposes a multi-camera optical tracking system that can be used for fusion of real-time 3D cardiac ultrasound volumes. The method compensates for the respiratory motion and uses wavelet fusion for combining pixels in the overlapping region. Qualitative and quantitative evaluation of the fused images from 6 volunteers showed improvement in image quality matrices proving that the approach was able to accurately fuse the images while improving the image quality.
Background: Epicardial adipose tissue (EAT) and coronary artery calcium (CAC) have been associated with incident coronary artery disease (CAD) and all-cause mortality in the general population. Their prognostic impact in HIV is unknown.

Methods: Observational study of 843 consecutive HIV-infected patients receiving antiretroviral therapy (ART) for at least 6 months risk stratified for cardiovascular disease at the Metabolic Clinic of the University of Modena and Reggio Emilia, Italy with coronary artery calcium (CAC) and EAT screening. Patients were followed for CAD and all-cause mortality for a median of 2.8 years accounting for a total of 2572 patient-year follow-up.

Results: Patients’ mean age was 50±8 years and 69% were men. At baseline EAT was associated with male gender, age, waist circumference, visceral adipose tissue, and lipodystrophy, while CAC>100 was associated with male gender, age and total cholesterol. During follow-up 33 patients suffered an event (15 incident myocardial infarctions and 18 deaths) and both EAT and CAC were larger in patients with events (p=0.038 and p=0.001 respectively). Multivariable regression analyses demonstrated that the upper tertile of EAT (>93 cm³; OR 2.15, 95% CI 1.06 – 4.39, p=0.034), and CAC>100 (OR 3.37, 95% CI 1.49 – 7.60, p=0.003) were independent predictors of events after adjusting for age and sex.

Conclusions: In this large cohort of HIV patients, EAT and CAC were independent predictors of hard outcomes after a median follow-up of approximately 3 years. This study supports the validity of ectopic fat and subclinical atherosclerosis as markers of risk in HIV infected patients.
DEVELOPMENT OF AN ALGORITHM TO IDENTIFY A PERIPHERAL ARTERIAL DISEASE COHORT USING ADMINISTRATIVE DATA

Yongzhe Hong, Meghan Sebastianski, Ross Tsuyuki, Michael Sean McMurtry

**Background:** Lower extremity peripheral arterial disease (PAD), diagnosed by an ankle-brachial index (ABI) ≤ 0.90, is an atherosclerotic disease that is underdiagnosed and undertreated. One of the main challenges facing PAD researchers is the lack of an accessible study cohort. PAD prevalence is <5% in the general population and about 10% in high risk patients, and the majority of patients are asymptomatic, making population studies both time consuming and expensive. We sought to evaluate whether case ascertainment using administrative health data would be a feasible way to identify PAD for epidemiologic research.

**Methods:** Three administrative databases from April 2002 to March 2012 were linked by personal healthcare number with the ABI scores from our two previous prospective studies. Alberta Inpatient Hospital Data and Ambulatory Care Data use ICD-10-CA/CCI codes. The Practitioner Payments Database uses ICD-9-CM codes. The validity of each code we proposed for PAD were calculated compared to the gold standard ABI scores ≤ 0.90. We also explored to validate the data with ABI ≤ 1, a more sensitive cut-off. Multivariate logistic regression was performed to investigate the risk factors for PAD. Different combinations of diagnostic codes and risk factors were explored to find out the best algorithms of identifying a PAD study cohort.

**Results:** Total of 1459 patients were included in our analysis. The average age was 63.5 years, and 66% were male. The highest sensitivity 34.7% was obtained by the algorithm of at least one ICD diagnostic code, with specificity 91.9%, Positive Predictive Value (PPV) 27.5% and Negative Predictive Value (NPV) 94.1%. The algorithm achieving the highest PPV 70% was age ≥70 years and at least one code within 443.9(ICD-9-CM), I73.9, I79.2 (ICD-10-CA/CCI) or all procedure codes, validated with ABI≤1 (sensitivity 5.38%, specificity 99.5% and NPV 82.9%).

**Conclusion:** Identifying a PAD study cohort using administrative data validated with ABI scores was insensitive, limiting the use of administrative data for epidemiologic research.
VASD-CLIN-2

SPEECH RECOGNITION ALGORITHMS IDENTIFY THE SECOND HEART SOUND IN PULMONARY HYPERTENSION

Tarek Kaddoura, Shine Kumar, Long Guo, Mohamed Elgendi, Daniel Kim, Dylan Taylor, Wane Tymchak, Dale Schuurmans, Roger Zemp, Ian Adatia

Background: We sought to use speech recognition algorithms to distinguish between S2 in subjects with and without pulmonary hypertension (PH).

Methods: We recorded simultaneously the heart sounds, electrocardiogram (EKG) and pulmonary artery (PA) pressure using the Zargis Signal X system (Princeton NJ). PH was defined by a mean pulmonary artery pressure (mPAp) ≥ 25 mmHg. We identified S2 by locating the loudest signal in a window (composed of 30% of the cardiac cycle) around the T wave on the simultaneously recorded EKG. We used the Matlab (2014b Mathworks, Natick MA) programming environment for signal analysis, optimization and training of an acoustic model for PH and non-PH based on Mel-Frequency Cepstral Coefficients. The developed acoustic models were tested against the remaining subjects using negative log likelihood classification.

Results: 129 patients (68 female) with a median age of 47 years (range 0.27-86) and median body surface area 1.73 m² met inclusion criteria. 125/129 subjects had recordings of sufficient quality for analysis. 68/125 subjects had PH (mPAp 37 mmHg, range 25-66) and 57/125 had normal mPAp 16 mmHg, range 9-24 (p<0.001). There was no difference in mPAp between the training and testing groups with PH (n=34, mPAp 38 mmHg, range 25-66 vs. n=34, mPAp 41 mmHg, range 25-63) (p=0.1) and without PH (n=30, mPAp 16 mmHg, range 9-24 vs. n=31, mPAp 16 mmHg, range 9-24) (p=0.4) respectively. The speech recognition algorithm correctly classified 78% of patients as PH or non-PH, with a false negative rate of 18%, and a false positive rate of 24%.

Conclusion: The results suggest that speech recognition algorithms based on S2 may differentiate subjects with and without PH. The false negative rate is concerning, but we hope to further improve it by integrating patient history into the algorithm.
CAROTID PLAQUE VOLUME CHANGES OF STROKE AND TIA PATIENTS IN SIX MONTH FOLLOW-UP PERIOD: OBSERVATIONAL STUDY WITH NEW THREE-DIMENSIONAL CAROTID ULTRASOUND

Hayrapet Kalashyan, Maher Saqqur, Ashfaq Shuaib, Helen Romanchuk, Thomas Jeerakathil, Khurshid Khan, Harald Becher

Background: Carotid plaque volume measured by Three-Dimensional Carotid Ultrasound (3DUS) is considered a reliable indicator of atherosclerosis burden. This is an observational, 6 months follow up study to determine the changes of carotid plaque volume in patients referred to Stroke Prevention Clinic after a cerebrovascular event.

Methods: Consecutive patients with a history of stroke or transient ischemic attack (TIA) were recruited for this study. All patients were on clinically indicated secondary prevention treatment based on current guidelines. Patients with internal carotid artery (ICA) occlusion or plaques extending beyond the ICA or with poor image quality were excluded.

New Single-Sweep 3D Ultrasound technique (Philips iU 22) equipped with volumetric transducer (vL 13-5) has been used to acquire images at baseline and follow-up (see Figure 1). The off-line volumetric measurements were performed using Q-Lab quantification software and employing the semiautomatic Stacked Ellipse method.

Recently our group has published the detailed methods used for acquisition and measurements. Inter-observer reproducibility was 5.6% ± 6.02%. Based on this, a change in plaque volume is considered real if it exceeds 12%.

Results: One hundred and sixteen patients (mean age 67.8±10.2 years, 36% women) and 232 carotid arteries were screened at baseline. Eighty eight patients had a history of hypertension (75.9%), 93 dyslipidemia (80.2%) and 24 diabetes mellitus (20.7%).

At this time 131 follow-up plaque volumes are available for analysis. At baseline, the mean PV was 0.337±0.31ml and at follow up 0.273±0.24ml, mean difference=0.064ml, p<0.001, (Paired-Samples T test, t=3.6, df=130). Regression (>12% reduction of plaque volume) was detected in 57 arteries (43.5%) and 20 arteries (15.3%) showed progression (>12% increase in plaque volume). The mean regression in plaque volume was 40.7%±20.5% and mean progression – 113.3%±186.6%.

Forty seven arteries (37.4%) showed no real change (between -12% to 12% change in plaque volume) and 5 arteries (3.8%) showed a new plaque.

Overall, 80.9% of plaque volumes regressed or remained unchanged (positive response) and 19.1% progressed or developed a new plaque (negative response). The positive response rate of the plaque volume to secondary prevention was significantly higher than the negative one: Chi-Square=50.1; df-1; p<0.001.

Conclusion: Using the new single sweep 3DUS technique, it is possible to detect plaque regression and progression at 6 months follow-up. In this group of stroke and TIA patients the plaque volume positively responds to the control of vascular risk factors by means of current secondary prevention measures.
INCREASED RELIANCE ON RIGHT ATRIAL ACTIVE EMPTYING AT DIAGNOSIS IS ASSOCIATED WITH CLINICAL WORSENING IN CHILDREN WITH PULMONARY ARTERIAL HYPERTENSION

Shine Kumar, Prashant Bobhate, Long Guo, Jean Trines, Mohammed Elgendi, Tarek Kaddoura, Shreepal Jain, Benjamin Goot, Tim Colen, Nee Khoo, Ian Adatia

**Background:** We sought to investigate the influence of right atrial (RA) active emptying fraction (RA EaF) on survival in childhood pulmonary arterial hypertension (PAH).

**Methods:** Children with PAH (mean PA pressure (mPAp) ≥ 25, wedge pressure < 15 mmHg) undergoing cardiac catheterization between 2009-14 were studied. RA and right ventricular (RV) endocardial areas indexed to BSA were traced in the apical 4 chamber view. We measured RA area at end systole (RAA max), at the onset of the P wave (RAA p) and end diastole (RAA min). We calculated the following: Right atrial fractional area change (RAFAC) from (RAA max – RAA min)/RAA max x 100, active RA emptying area (RA Ea) from RAA p – RAA min, and RA EaF from (RA Ea/RAFAC) x 100. Time to clinical worsening was calculated from diagnosis to initiating prostanoid therapy, transplant or death.

**Results:** We studied 31 children (16 females), mean age 6.7±5.6 years and mean BSA 0.83±0.45 m2. Median follow up was 1.9 years (range 0.1-6.1). Median event free survival was 1.2 years (range 0.01-5.5) with 12 events due to worsening of PAH (10 patients started on prostanoid, 3 deaths, 1 transplant). RA EaF ≥ 56% predicted worse diagnostic hemodynamics (mPAp 65±22 mmHg vs. 42±18 mmHg (p = 0.004), PVRI 16.8±8 vs. 9.9 ± 6.3 WU.m2 (p=0.01)) and significant clinical worsening in 10/19 (53%) compared to RA EaF <56 (2/12 (17%), p = 0.03). A higher dependency on RA EaF at diagnosis predicted 5 year clinical worsening (sensitivity 83%, specificity 53%). RVFAC <25% predicted 5 year clinical worsening with 67% sensitivity and 68% specificity and combining the variables predicted clinical worsening with 80% sensitivity and 91% specificity.

**Conclusion:** Increased reliance on active RA emptying is associated with clinical worsening in childhood PAH. RA EaF supplements RVFAC in predicting clinical worsening.
Dr. Joseph Dvorkin Memorial Lecture

Joseph Dvorkin, B.A., M.D., FRCP(C), FACP, FACC (1917-1976) was born in Calgary, and received his M.D. Degree from the University of Alberta in 1943. After discharge from the R.C.A.M.C. in 1945 with the rank of Major, he was appointed as a Clinical Professor at the University of Alberta. A pioneer in heart care, he belonged to the team of physicians who initiated diagnostic cardiology and who were involved in Canada’s first open heart surgery procedure at the University of Alberta Hospital. The principles he lived by were professional commitment, integrity, and honesty, thus fulfilling his quest to ease the suffering of his fellow man.

The Dvorkin lectureship is awarded to a renowned speaker for the Mazankowski Cardiac Sciences Research Day/Medicine Grand Rounds.

PAST INVITED SPEAKERS:
2014 - Benoit Bruneau, PhD, Toronto Western Hospital
2013 - Francis G. Spinale, MD, PhD
   University of South Caroline School of Medicine
2012 - Dr. John R. Teerlink, University of California
2011 - Dr. Thomas G. Parker, University of Toronto
2010 - Dr. John E. Hall, University of Mississippi
2009 - Dr. Kenneth Walsh, Boston University
2008 - No recipient – Mazankowski Alberta Heart Institute
   Inaugural Congress
2007 - Dr. Stephen Frames, Sunnybrook HSC
2006 - Dr. Michael Bliss, University of Toronto
2005 - Dr. Matthias Friedrich, University of Calgary
2004 - Dr. William Ghali, University of Calgary
2003 - Dr. D. George Wyse, University of Calgary
2002 - Dr. Duncan Stewart, University of Toronto
2001 - Dr. Bernard Gersh, Mayo Clinic
2000 - Dr. Lyall Higginson, University of Ottawa Heart Institute
Audrey Greenough-Norm Davies Award

Dr. Norm Davies was an outstanding cardiologist at the University of Alberta Hospitals who died a sudden and tragic death at the age of 37 years. Dr. Davies was a superb teacher, an excellent researcher and a doctor who looked after his patients in an ideal manner. He blended his great intellectual gifts with compassion and caring in a unique combination. The Dr. Norman Davies Memorial Fund was established to help continue and promote Dr. Davies’ work in research, education and patient care. Mrs. Audrey Greenough and Mrs. Beth Leisch donated the funds for this award. The Norm Davies Award is awarded for the best abstract presented by a Medical Resident at the Mazankowski Cardiac Sciences Research Day.

PAST AWARD WINNERS:

2014 - Dierdre O’Neill
2013 - Dr. Vikran Gurtu
2012 - Dr. Aws Alherbish
2011 - Dr. Mikael J. Hanninen
2010 - Dr. Sean van Diepen
2009 - Dr. Mustafa Toma
2008 - Dr. Michael Tjandrawidjaja
2007 - Dr. Kevin Bainey
2006 - Dr. Justin Ezekowitz
2005 - Dr. Michael McDonald
2004 - Dr. Michael McDonald
2003 - Dr. Taha Taher
2002 - Dr. Raymond Leung
2001 - Dr. Bernard Thebaud & Dr. Bernardo V. Alvarez
Dr. Francis X. Witkowski Award

Dr. Francis Witkowski was an innovative scientist who was on the cutting edge of technology. Dr. Witkowski was a world leader in mapping the electrical alterations that occur in the heart during ventricular fibrillation. His advances in the use of optical imaging to map cardiac electrical activity provide an important new approach to the study of ventricular fibrillation. To remember and honour this innovative approach to science the Cardiovascular Research Group and the Division of Cardiology of the Faculty of Medicine, University of Alberta have created the Dr. Francis X. Witkowski Publication Award.

The Dr. Francis X. Witkowski Award is given to a young investigator and will favour innovative or technologically based science.

PAST AWARD WINNERS:

2014 - Valibhav B. Patel, PhD, Postdoctoral Fellow, Dept of Medicine
2013 - Peter Dromparis, Medical Student
2012 – Dr. Vijay Kandalam
2011 - Dr. Mohammad Ali
2010 - Dr. Gopinath Sutendra
2009 - Dr. Vernon Dolinsky
2008 - Dr. Debby P.Y. Koonen
2007 - Dr. Jayan Nagendran
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