MAZANKOWSKI CARDIAC SCIENCES RESEARCH DAY

KATZ GROUP CENTRE FOR PHARMACY AND HEALTH RESEARCH
UNIVERSITY OF ALBERTA
JUNE 9th, 2017

CSRESEARCHDAY.COM
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ACKNOWLEDGEMENTS

CARDIAC SCIENCES RESEARCH DAY
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Dr. Nadia Jahroudi
Dr. Gary Lopaschuk

Dr. Sean McMurtry
Dr. Jeevan Nagendran
Dr. Sean Van Diepen
June 9, 2017

Dear Colleagues,

Every year we celebrate the success of our trainees and honour their mentors: once again welcome to the 21st Annual Cardiac Sciences Research Day. Trainees from both the basic and clinical sciences will be presenting numerous interesting abstracts on different topics in cardiovascular medicine, as living proof of the productivity and vitality of our cardiovascular department.

We are joined in our celebrations by two brilliant speakers:

**Dr. James de Lemos, MD**
Professor of Medicine
UT Southwestern Medical Center
Dallas, TX, United States
Dr. de Lemos will be presenting
*Predicting Cardiovascular Disease Risk Among Apparently Healthy Adults: Can We Build a Better Mousetrap?*

**Dr. Phillip McFarlane, MD, FRCP(C), PhD**
Assistant Professor, Division of Nephrology
St. Michael's Hospital, University of Toronto
Toronto, ON, Canada
Dr. McFarlane will be presenting:
*Changes in the Hypertension Canada Guidelines That Will Change Your Practice*

I would like to extend my thanks to all the colleagues who helped in the organization of this day (judges, chairs, administrative assistants) and to the industry sponsors who gave generously to support us. Without their support this important initiative would be very difficult to stage. A special recognition is owed to the University Hospital Foundation that has relentlessly supported research initiatives at the MAZ for years and has again donated generously to make this celebration possible.

Please join me in the poster area and conference room throughout the day and for a closing reception in the atrium after the award ceremony.

Warm regards,
Paolo Raggi, MD, FACC, FACP, FASNC
Chair, CSRD Organizing Committee
21ST ANNUAL MAZANKOWSKI CARDIAC SCIENCES RESEARCH DAY
0745 – 1730 | FRIDAY, JUNE 9, 2017
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

0800 - 0900  Medical Grand Rounds & Dr. Joseph Dvorkin
Memorial Lecture Presenter
James de Lemos, MD
Professor of Medicine, UT Southwestern Medical Center,
Dallas, Texas, United States

Topic: Predicting Cardiovascular Disease Risk
Among Apparently Healthy Adults:
Can We Build a Better Mousetrap?

0900 - 1000  Coffee Break / Poster Viewing

1000 - 1130  Podium Abstract Session
Chairs – Dr. Sean McMurtry
& Dr. Gary Lopaschuk

1000  Ahmed M. Darwesh, Mona F. El-Azab,
Noha M. Abo-Gresha, Norhan M. El-Sayed,
Yasser M. Moustafa
Cardioprotective Mechanisms of Exenatide in
Isoprenaline-Induced MI: Novel Effects On Myocardial
α-Estrogen Receptor Expression and IGF/IGF-2 System

1015  Sabin J. Bozso, Jeevan Nagendran, Colleen M. Norris,
Finlay A. McAlister, Jehangir J. Appoo, Michael C. Moon,
Darren H. Freed, Jayan Nagendran
Coronary Artery Bypass Grafting Provides a Long-Term
Survival Benefit Over Multivessel Percutaneous Coronary
Intervention in Patients with Diabetes and Left Ventricular
Dysfunction: A 12-Year Propensity Matched Analysis
1030  **Yumna Zia**, Ala A. Rajabi, Kelly A. Leonard, Si Mi, Yuan-Yuan Zhao, Catherine J. Field, Jonathan Curtis, Jelske N. van der Veen, René L. Jacobs  
*Hepatic PEMT Expression, But Not Dietary Choline, Reverses the Protection Against Atherosclerosis in Pemt"/-/Ldlr"/- Mice*

*Utilization and Impact of Cardiac Rehabilitation in Premature and Non-Premature Coronary Artery Disease*

*Distinctive Functions of PI3Kα² in Endothelial Cells and Cardiomyocytes in Response to Myocardial Infarction: Implications for Targeting PI3Kα² in Myocardial Infarction Treatment*

*Right Ventricular Function and Remodeling Predict Outcome in Patients with Heart Failure Phenotypes*

1130 - 1250  **Lunch / Poster Viewing**

1255 - 1300  **Introduction - Visiting Professor, Cardiac Sciences Research Day – Dr. Paolo Raggi**

1300 - 1400  **Philip McFarlane, MDm FRCP(C), PhD**  
Assistant Professor, Division of Nephrology, St. Michael’s Hospital, University of Toronto, Toronto, Canada  
*Topic: Changes in the Hypertension Canada Guidelines That Will Change Your Practice*

1415 - 1515  **Podium Abstract Session**  
**Chairs – Dr. Sean Van Diepen & Dr. Nadia Jahroudi**

1415  **Mengcheng Shen**, Zameaneh Kassiri  
*Cell-Specific and Pharmacological Inhibition of Disintegrin and Metalloproteinase 17 Attenuates Experimental Thoracic Aortic Aneurysms*

1430  **Ricky Turgeon**, Glen Pearson, Michelle Graham  
*Pharmacological Treatment of Patients with Angina with No Obstructive Coronary Artery Disease (Anoca): A Systematic Review*
1445  Nader S. Aboelnazar, Sayed Himmat, Sanaz Hatami, Mohamad S. Burhani, Christopher W. White, Peter Dromparis, Michael Mengel, Darren H. Freed, Jayan Nagendran
*Improved Outcomes with Negative Pressure Ventilation (NPV) During Normothermin Ex Vivo Lung Perfusion*

1500  Andrea Joy Van Damme, Colleen Norris, David Buijs, Caroline Black, Kara Penney, Gabor Gyenes
*The Impact of Prehabilitation On Functional Capacity and Quality of Life for Patients Awaiting Coronary Artery Bypass Graft Surgery and/or Mitral Valve Surgery*

1515 - 1530  **Coffee Break / Poster Viewing**

1530 - 1630  **Podium Abstract Session**
*Chairs – Dr. Jeevan Nagendran & Dr. Bibiana Cujec*

1530  Kim Ho, Cory Wagg, Liyan Zhang, Jody Levasseur, Jason R.B. Dyck, John R. Ussher, Gary D. Lopaschuk
*The Contribution of Fatty Acid and Ketone Body Oxidation to Energy Production Increases in the Failing Heart and is Associated with a Decrease in Cardiac Efficiency*

1545  M. Florencia Ricci, Billie-Jean Martin, Ari Joffe, Gwen Bond, Irina Dinu, Gonzalo Garcia Guerra, Charlene Robertson
*Deterioration of Functional Abilities in Children Surviving the Fontan Operation*

1600  Bruno Saleme, Vikram Gurtu, Adam Kinnaird, Aristeidis Boukouris, Corey Wagg, Gary D. Lopaschuk, Gopinath Sutendra
*Differential Regulation of P53 By Pyruvate Kinase M2 Can Be Therapeutically Targeted in Chemotherapy-Induced Cardiotoxicity*

1615  Nariman Sepehrvand, Yinggan Zheng, Paul W. Armstrong, Robert Welsh, Justin A. Ezekowitz
*Identifying Low-Risk Patients for Early Discharge From Emergency Department Without Using Subjective Descriptions of Chest Pain*

1630 - 1700  **Abstract Judging, Awards Ceremony & Closing Remarks**

1700  Reception
GUEST SPEAKER BIOGRAPHIES
JAMES de LEMOS, MD

Dr. de Lemos is Professor of Medicine at UT Southwestern Medical Center and holds the Sweetheart Ball-Kern Wildenthal, MD, PhD Distinguished Chair in Cardiology. He graduated from Harvard Medical School and completed an Internal Medicine Residency at UT Southwestern Medical Center, where he also served as Chief Medical Resident. He completed a fellowship in Cardiovascular Medicine and served on the faculty at the Brigham and Women’s Hospital before returning to UT Southwestern Medical School. He has served as the Cardiology Service Chief at Parkland Memorial Hospital, and the Cardiology Fellowship Director at UT Southwestern. He has held positions on multiple committees of the AHA and ACC, including the STEMI Guideline Committee, and as Chair of the Research and Publications Committee for the NCDR ACTION-GWTG registry. He is a standing member of the FDA’s Cardiorenal Advisory Panel. He is now the Executive Editor for Circulation, and has previously served on the editorial boards of the Journal of the American College of Cardiology, the American Journal of Cardiology and the American Heart Journal. His primary research interests are in early detection, risk assessment and management of cardiovascular disease, with a particular focus on the role of cardiovascular biomarkers. His research has evaluated existing biomarkers such as B-type natriuretic peptide, C-reactive protein and cardiac troponins as well as novel biomarkers reflecting biological pathways of disease. He was the lead author of the Z phase of the A to Z trial, an international trial investigating different cholesterol lowering strategies in patients with acute coronary syndromes. He has mentored >30 post-doctoral research trainees and has authored or coauthored over 300 manuscripts and book chapters. He has won several teaching and mentorship awards, including the 2015 Women in Cardiology Mentoring Award by the AHA. He has been elected to the Association of University Cardiologists and the American Society of Clinical Investigation.
PHILLIP McFARLANE, MD, FRPC(C), PhD

Dr. Phil McFarlane is a clinical-investigator in the Division of Nephrology at St. Michael’s Hospital in Toronto, and an assistant professor at the University of Toronto. At St. Michael’s he is the Medical Director of Home Dialysis and the Chief Nephrologist in the Live Kidney Donor Program. He is a member of the Diabetes Canada Clinical Practice Guidelines group, the Canadian Society of Nephrology guideline group, and the Hypertension Canada guideline group. He has completed his Ph.D. in health economics at the Institute for Medical Sciences at the University of Toronto. His areas of research interest include health economics and outcomes research. He is currently the Provincial Medical Lead for dialysis access and home hemodialysis. He has published over 90 peer-reviewed manuscripts and three book chapters.
ORAL ABSTRACTS
CARDIOPROTECTIVE MECHANISMS OF EXENATIDE IN ISOPRENALINE-INDUCED MI: NOVEL EFFECTS ON MYOCARDIAL α-ESTROGEN RECEPTOR EXPRESSION AND IGF-1/IGF-2 SYSTEM

Ahmed M. Darwesh, Mona F. El-Azab, Noha M. Abo-Gresha, Norhan M. El-Sayed, Yasser M. Moustafa

Background: Myocardial infarction (MI) is one of the main causes of morbidity and mortality in diabetic patients. The antidiabetic glucagon-like polypeptide-1 receptor (GLP-IR) agonists, like exenatide, proved to confer cardioprotection; however, their exact mechanisms are not fully elucidated. Although the cardioprotective effect of α-estrogen receptor (ERα) is well established, its involvement in exenatide-induced cardioprotection has never been investigated. Moreover, modulation of insulin-like growth factor-1/2 (IGF-1/IGF-2) system by exenatide, and the consequent effect on cardiomyocyte apoptosis, is yet to be established. Therefore, current study aimed to investigate the cardioprotective potential of exenatide versus the standard cardioprotective agent, 17β-estradiol, against isoprenaline (ISO)-induced MI in rats.

Methods: Sprague-Dawley male rats were treated with exenatide and/or 17β-estradiol for 8 weeks followed by acute MI induction using s.c. injection of ISO on two successive days at the end of the study period. Electrocardiography (ECG) was recorded 24 hours after the second dose of ISO. Myocardial and left ventricle weight indices were calculated to assess the extent of hypertrophy. Serum levels of IGF-2 and cardiac markers, represented by total CK, CK-MB and LDH, were also determined. Histopathological examination was done to investigate the extent of MI in left ventricles. Alpha estrogen, IGF-1 and IGF-2 receptors expression in the left ventricle were determined immunohistochemically.

Results: MI-insulted group showed ECG abnormalities represented by Q wave depression, ST segment elevation, and QT interval prolongation, elevated serum cardiac markers, higher serum IGF-2 levels along with histopathological abnormalities. Furthermore, myocardial and left ventricular weight indices indicated a marked hypertrophy in MI rats. Pretreatment with exenatide and/or 17β-estradiol ameliorated these anomalies with maximum cardioprotection achieved with combined treatment. This was associated with up-regulation of both ERα and the anti-apoptotic IGF-1R, and down-regulation of the apoptotic IGF-2R in left ventricles. Inhibition of ERs in Langendorff preparations confirmed their involvement in mediating exenatide-induced cardioprotective effect.

Conclusion: Current study showed for the first time that GLP-1R agonism exerted cardioprotection through up-regulation of ERs along with modulation of IGF-1/IGF-2 signaling in the favor of anti-apoptosis. Moreover, the combined treatment elicited more favorable cardioprotection, which may be ascribed to an increase in IGF-2 that may act on markedly upregulated anti-apoptotic IGF-1R, leaving the expression of the apoptotic IGF-2R unchanged at a low level. Interestingly, the recent development of GLP-1-estradiol conjugate molecule with selective anti-diabetic and anorexiant effects; yet, lacking the undesirable properties of general estrogen treatment, represents a promising approach for developing selective cardioprotective agents. Therefore, we propose that the synergistic action of exenatide and 17β-estradiol in combination may provide a novel therapy for MI particularly in diabetic patients.
CORONARY ARTERY BYPASS GRAFTING PROVIDES A LONG-TERM SURVIVAL BENEFIT OVER MULTIVESSEL PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH DIABETES AND LEFT VENTRICULAR DYSFUNCTION: A 12-YEAR PROPENSITY MATCHED ANALYSIS

Sabin J. Bozso, Jeevan Nagendran, Colleen M. Norris, Finlay A. McAlister, Jehangir J. Appoo, Michael C. Moon, Darren H. Freed, Jayan Nagendran

Background: Although the role of coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) in patients with diabetes (DM) and multivessel coronary artery disease has been established by randomized controlled trials, these trials have generally excluded patients with left ventricular dysfunction (LVD). The purpose of this study was to compare the outcomes of patients with multivessel CAD, DM and LVD undergoing PCI or CABG.

Methods: In this propensity-matched study, the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry was used to compare outcomes for patients with multivessel CAD, DM, and LVD treated with PCI or CABG between 2004 and 2016. Patients were further stratified by LVEF: 35-49% and <35%. The primary outcome was major adverse cardiac and cerebrovascular events (MACCE) defined as the composite of death, stroke, myocardial infarction (MI), and repeat revascularization. Secondary outcomes were the individual components of the primary composite end-point. Among 2837 eligible patients, 869 PCI patients and 869 CABG patients were propensity matched.

Results: At mean follow-up of 5.5-years, PCI as compared with CABG was associated with a significantly higher risk of MACCE in both the EF 35-49% (p<0.001) and EF <35% (p<0.001) cohorts. Similarly, PCI compared to CABG was associated with an increased risk of death in both the EF 35-49% cohort (p=0.001) and the EF <35% (p=0.002) cohort. Incidence of stroke did not differ between PCI and CABG in either the EF 35-49% (p=0.663) or EF <35% cohorts (p=0.630). Rates of MI were similar between PCI and CABG in the EF 35-49% cohort, however, PCI was associated with an increased rate of MI in the EF <35% cohort (p=0.001). Repeat revascularization occurred more frequently in those treated with PCI in both the EF 35-49% cohort (p<0.001) and the EF <35% cohort (p<0.001).

Conclusion: At long term follow up, patients with multivessel CAD, DM and LVD treated with CABG exhibited significantly lower incidence of MACCE and better long-term survival over PCI, without a higher risk of stroke.
110,655 Patients in Alberta underwent coronary angiography for coronary artery disease for the first time in 2004-2016

107,818 Were excluded
- 71,826 Did not have multivessel coronary artery disease
- 26,344 Did not have a diagnosis of diabetes mellitus
- 3,038 Underwent exclusively medical management
- 6,610 Had a left ventricular ejection fraction greater than 50%

2,837 Were included in study analysis
- 1,556 Underwent PCI
- 1,281 Underwent isolated CABG

1,738 Were included in propensity-score matched analysis
- 869 Underwent PCI
- 869 Underwent isolated CABG

Figure 1. Study Population.
CABG denotes coronary-artery bypass graft surgery, and PCI percutaneous coronary intervention.
Figure 2. Cumulative Risks of the Study Outcomes in the Ejection Fraction 35-49% Cohort

A. MACCE

B. Death

C. Stroke

D. Myocardial Infarction

E. Repeat Revascularization

- **A** MACCE: First treatment post index cath
  - p = 0.001

- **B** Death: First treatment post index cath
  - p = 0.01

- **C** Stroke: First treatment post index cath
  - p = 0.96

- **D** Myocardial Infarction: First treatment post index cath
  - p = 0.12

- **E** Repeat Revascularization: First treatment post index cath
  - p = 0.001
Figure 3. Cumulative Risks of the Study Outcomes in the Ejection Fraction <35% Cohort

A MACCE

B Death

C Stroke

D Myocardial Infarction

E Repeat Revascularization
Table 1. Baseline Characteristics before Propensity Matching

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<tr>
<td><strong>EF 35-49%</strong></td>
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<tr>
<td>MACCE</td>
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<tr>
<td>Death</td>
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<tr>
<td>Myocardial Infarction</td>
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<tr>
<td>Repeat</td>
<td></td>
<td></td>
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<tr>
<td>Revascularization</td>
<td>5.17</td>
<td>3.65</td>
<td>7.3</td>
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<tr>
<td><strong>EF &lt;35%</strong></td>
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<tr>
<td>MACCE</td>
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<tr>
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<td>0.52</td>
<td>2.49</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
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<td>1.58</td>
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<tr>
<td>Repeat</td>
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<tr>
<td>Revascularization</td>
<td>5.35</td>
<td>3.17</td>
<td>9.02</td>
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HEPATIC PEMT EXPRESSION, BUT NOT DIETARY CHOLINE, REVERSES THE PROTECTION AGAINST ATHEROSCLEROSIS IN PEMT\(^{-/-}\)/LDLR\(^{-/-}\) MICE

Yumna Zia, Ala A. Rajabi, Kelly A. Leonard, Si Mi, Yuan-Yuan Zhao, Catherine J. Field, Jonathan Curtis, Jelske N. van der Veen, René L. Jacobs

**Background:** Phosphatidylethanolamine N-methyltransferase (PEMT) is a hepatic enzyme that converts phosphatidylethanolamine (PE) to phosphatidylcholine (PC). Hepatic PC is required for the synthesis of hepatic membranes, bile, very low-density lipoprotein secretion and de novo choline synthesis. Mice lacking PEMT (Pemt\(^{-/-}\)) are protected from diet induced obesity and insulin resistance, a phenotype that is reversed by choline supplementation. PEMT deficiency also reduces plasma lipids and provides protections against atherosclerosis in low-density lipoprotein receptor deficient (ldlr\(^{-/-}\)) mice and Apoe\(^{-/-}\) deficient mice. Additionally, recent publications have demonstrated that dietary choline can be metabolized by gut microbiota into trimethylamine-N-oxide (TMAO), a novel risk marker for atherosclerosis. The objective of this study was to determine if restoring PEMT expression promotes atherosclerosis and to examine the effect of choline supplementation on TMAO production and atherosclerosis in Pemt\(^{-/-}\)/Ldlr\(^{-/-}\) mice.

**Methods:** Pemt\(^{+/+}\)/Ldlr\(^{-/-}\) (SKO) and Pemt\(^{-/-}\)/Ldlr\(^{-/-}\) (DKO) mice were injected with an adeno-associated virus (AAV) vector containing the cDNA for green fluorescent protein (GFP) (control) or human PEMT enzyme, and fed a western diet (40% calories from fat, 0.5% cholesterol) for 8 weeks. In a second experiment, SKO and DKO mice were fed a western diet containing 3 or 10g/kg choline for 12 weeks.

**Results:** DKO mice were protected against atherosclerosis; reintroduction of PEMT via AAV normalized atherosclerosis in DKO mice. The increase in atherosclerosis in PEMT-injected DKO mice was associated with an increase in plasma lipids and TMAO. In the second experiment, choline supplementation (CS) increased plasma TMAO levels but did not increase atherosclerosis or plasma lipids in in DKO mice. Additionally, CS did not significantly alter the abundance of different bacterial species in the gut microbiome, indicating that dietary choline did not regulate the microbial diversity in the gut.

**Conclusion:** Reintroducing hepatic PEMT reverses the atheroprotective phenotype of DKO mice, increases plasma lipids and TMAO production. This is the first report demonstrating de novo choline synthesis may also regulate TMAO production. CS in DKO mice increases TMAO production but not atherosclerosis and plasma lipids. Our data suggests that TMAO correlates with atherosclerosis only in the presence of elevated lipids.
UTILIZATION AND IMPACT OF CARDIAC REHABILITATION IN PREMATURE AND NON-PREMATURE CORONARY ARTERY DISEASE

Michael Khoury, James A. Stone, Danielle A. Southern, Stephen B. Wilton, Diane Galbraith, Sandeep Aggarwal, Ross Arena, Billie-Jean Martin

Background: With improved survival from acute coronary syndromes, increasing importance is being placed upon proven secondary prevention strategies, such as cardiac rehabilitation (CR). Premature coronary artery disease (premCAD), defined as the first manifestation of CAD in men <55yo and women <65yo, is increasing in incidence. However, few studies have evaluated the utility of CR in the premCAD population. We sought to evaluate the utilization of CR and the associations between CR completion and mortality in individuals with premCAD.

Methods: All patients with CAD referred to the Total Cardiology-Cardiac Wellness program in Calgary, Canada between 1996 and March 2016 were included. Additional covariate and survival data were obtained from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database. All patients referred were offered a 12-week, comprehensive CR program with exercise testing at start and completion. Baseline covariates were compared between those with and without premCAD. The association between premCAD diagnosis and CR completion was assessed using adjusted logistic regression; the association between CR completion and survival was assessed using adjusted Cox proportional Hazards Models, stratified by premCAD diagnosis.

Results: A total of 23,215 patients were referred to CR, 8,383 (36.1%) with premCAD (68.7% male, mean age 50.2 (SD 6.9) years). PremCAD patients had a significantly different cardiometabolic risk factor profile and were more likely to be of South Asian descent than those with non-premCAD (Table). PremCAD patients were more likely to complete CR (53.8% vs 50.4% completion; adjusted odds ratio for completion 1.27, 95% CI 1.20, 1.35). While premCAD patients had greater baseline exercise capacity [8.3 (SD 2.0) vs 7.2 (SD 2.0) Metabolic Equivalents (METs), p<0.0001], both groups had similar improvements over the course of CR (0.93 vs 0.95 METs, p=0.093). Median follow-up was 7.2 years (intra-quartile range, 3.9, 11.4), and there were 3,510 deaths. PremCAD patients derived a greater survival benefit from CR (adjusted hazard ratio (HR) 0.55 (95% CI 0.47, 0.65) compared with non-premature CAD (adjusted HR 0.65 (95% CI 0.60, 0.70) (Figure).

Conclusion: PremCAD patients possess a unique cardiometabolic risk factor profile compared with non-premature CAD patients. Patients with premCAD are more likely to complete CR and derive a greater survival benefit from CR compared with non-premature CAD patients. However, nearly half of all referred patients fail to complete CR. Therefore barriers to CR completion must be addressed to optimize long-term outcomes, particularly in younger populations where CR may yield greater improvements for a longer period.
Figure. Survival stratified by Premature Coronary Artery Disease (PremCAD) diagnosis and CR completion. PremCAD patients who completed CR exhibited the best survival. CR inferred a greater benefit in patients with premCAD compared to those with non-premature CAD.
Table: Selected baseline population characteristics by Premature CAD status. CR: Cardiac Rehabilitation; BMI: Body Mass Index

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=23215)</th>
<th>Non-Premature CAD (n=14832)</th>
<th>Premature CAD (n=8383)</th>
<th>p-value</th>
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<tr>
<td>Completed CR (%)</td>
<td>11981 (51.6%)</td>
<td>7468 (50.4%)</td>
<td>4513 (53.8%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>South Asian (%)</td>
<td>1920 (8.3%)</td>
<td>1173 (7.9%)</td>
<td>747 (8.9%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Male (%)</td>
<td>18207 (78.4%)</td>
<td>12453 (84.0%)</td>
<td>5754 (68.6%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mean age, years (SD)</td>
<td>61.3 (11.3)</td>
<td>67.5 (7.9)</td>
<td>50.2 (6.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension (%)</td>
<td>14534 (62.6%)</td>
<td>10088 (68.0%)</td>
<td>4446 (53.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>15743 (67.8%)</td>
<td>10217 (68.9%)</td>
<td>5526 (65.9%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes Mellitus (%)</td>
<td>5178 (22.3%)</td>
<td>3634 (24.5%)</td>
<td>1544 (18.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive family history (n=21252, %)</td>
<td>6281 (29.6%)</td>
<td>3714 (27.2%)</td>
<td>2567 (33.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>1366 (5.9%)</td>
<td>1026 (6.9%)</td>
<td>340 (4.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular Disease (%)</td>
<td>1120 (4.8%)</td>
<td>888 (6.0%)</td>
<td>232 (2.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>6240 (26.9%)</td>
<td>2838 (19.1%)</td>
<td>3402 (40.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²) at referral (mean, SD) (n=21137)</td>
<td>28.8 (8.9)</td>
<td>28.5 (9.1)</td>
<td>29.5 (8.5)</td>
<td>&lt;0.0001</td>
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DISTINCTIVE FUNCTIONS OF PI3KΒ IN ENDOTHELIAL CELLS AND CARDIOMYOCYTES IN RESPONSE TO MYOCARDIAL INFARCTION: COMPLICATIONS FOR TARGETING PI3KΒ IN MYOCARDIAL INFARCTION TREATMENT

Xueyi Chen, Jessica DesAulniers, Xiuhua Wang, Abul Kalam Azad, Allan G. Murray, Zamaneh Kassiri, Bart Vanhaesebroeck, Gavin Y. Oudit

Background: Myocardial infarction (MI) and the following cardiac remodeling are associated with high mortality and morbidity rates worldwide, and multiple cell types and signaling cascades contribute to the processes of remodeling. PI3Kβ, an isoform of class IA PI3K, has been suggested to be a new target for anti-thrombotic therapy. In this study, we examined the function of PI3Kβ in endothelial cells and cardiomyocytes after MI to unveil the potential of targeting PI3Kβ in MI treatment.

Methods: Mice with kinase-dead p110β expressed specifically in cardiomyocytes (p110β-αMHC) or endothelial cells (p110β-Tie2) were generated; p110βFlx was used as littermate controls. Intraperitoneal injection of Tamoxifen (2mg/mouse for 5 days) was given to p110β-Tie2 to activate kinase-dead p110β expression two weeks before experiments. Sham- or MI-operation on mice was performed in a blinded fashion. Cardiac function was assessed by echocardiography and mortality data were collected. Triphenyl tetrazolium chloride (TTC), CD31, and wheat germ agglutinin (WGA) staining were performed to examine the infarct size, vascular density, and hypertrophy on 7-day post-operated mice. Signaling pathways were assessed by Western blotting.

Results: Loss of p110β activity in endothelial cells resulted in increased survival rate, decreased infarct size, and higher vascular density in peri-infarct area, resulting in preservation of systolic function after MI compared to controls. Increased phosphorylation of Akt was detected in p110β-Tie2 hearts. Culturing the HUVEC, we confirmed that the decrease of p110β caused an increase of Akt activation. In contrast, inactivation of p110β in cardiomyocytes increased MI-related mortality, infarct size, and hypertrophic level with reduced vascular density, leading to deterioration of systolic function. And the adverse ventricular remodeling was correlated with an increase of apoptotic cardiomyocytes after MI-operation.

Conclusion: Inhibition of endothelial p110β improves cardiac performance after MI, possibly through feedback mechanisms leading to activation of pAkt by other PI3K isoforms. Conversely, cardiomyocyte p110β is required to maintain cardiac function following MI. These results indicate the importance of cell-type specific of PI3Kβ signaling in the response to heart disease.
RIGHT VENTRICULAR FUNCTION AND REMODELING PREDICT OUTCOME IN PATIENTS WITH HEART FAILURE PHENOTYPES


Background: Right ventricular (RV) abnormalities are increasingly associated with poor clinical outcomes however their prevalence and prognostic implications among the spectrum of patients with heart failure (HF) has not been well characterized.

Methods: 89 healthy controls (47 male and mean age 57 ± 10) and 468 patients (300 male and mean age 56 ± 16, 214 patients at ACC/AHA HF Stage B and 254 at Stage C) with predefined HF phenotypes underwent a standard cardiac magnetic resonance (CMR) examination. Ventricular volumes were traced from cine imaging and data from healthy controls was used to define normal. Regression analyses were used to determine significant CMR predictors of outcome. A primary composite outcome consisted of all-cause mortality and HF hospitalization.

Results: Among all patients, RV dysfunction (RVD) was found in 48%, RV enlargement (RVE) in 38%, and any RV abnormality in 61%. During a mean follow-up of 962 ± 616 days, 75/468 patients had an outcome event. A basic model, including age, coronary artery disease, hypertension, diabetes mellitus, chronic renal failure, and chronic obstructive pulmonary disease, was constructed and played an adjusting effect for CMR parameters in multivariate model. CMR-derived LV and RV ventricular volumes and RV function predicted outcome in both univariate and multivariate model. RVE had incremental prognostic value over LV volume and mass. Furthermore, RV volume and function additionally predicted outcome over indexed LV mass.

Conclusions: RV abnormalities are prevalent among patients with HFREF and HFPEF phenotypes. RVE have additional prognostic value over conventional LV parameters. Routine assessment of RV on CMR is recommended in all cases of possible HF.
Figure 2. Additive Prognostic Value of CMR Measures in Heart Failure Cohort
Incremental $\chi^2$ score by stepwise inclusion of indexed LV mass, RVE or RVESVi in addition basic model in Cox proportional hazard regression models among patients overall.
CELL-SPECIFIC AND PHARMACOLOGICAL INHIBITION OF DISINTEGRIN AND METALLOPROTEINASE 17 ATTENUATES THORACIC AORTIC ANEURYSMS

Mengcheng Shen, Zamaneh Kassiri

Background: Disintegrin and metalloproteinase 17 (ADAM17) is involved in embryonic development, cellular signaling, and inflammation by ectodomain shedding of a wide variety of transmembrane proteins, such as cytokines, chemokines, growth factors, adhesion molecules and receptors. Aortic aneurysm, focal dilation and weakening of the aortic wall, is chronically formed and developed as a result of destructive extracellular matrix (ECM) remodeling, inflammatory cell infiltration, and smooth muscle cell (SMC) depletion. Increased ADAM17 levels have been observed in aneurysmal tissues from patients and animal models. However, whole body ADAM17 deficiency is embryonically lethal, as such the role of ADAM17 in the pathogenesis of thoracic aortic aneurysm (TAA) has remained unclear.

Methods: ADAM17 protein levels and distribution patterns in human TAA and control aortas were evaluated by immunoblotting and immunohistochemistry (IHC). To investigate the role of SMC-specific deletion of ADAM17 in TAA formation and progression, mice lacking ADAM17 in their SMC (Adam17$^{flox/flox}$/Sm22Cre, Adam17$^{SMC}$) and littermates with intact ADAM17 levels (control, Adam17$^{flox/flox}$, Adam17$^{f/f}$) were subjected to an experimental model of TAA. Anesthetized mice underwent thoracotomy followed by periadventitial application of elastase (30 U/ml) or saline for 5 min. TAA formation and expansion were assessed at day 3 and 14 post surgery. Aortas underwent histological examination, IHC staining and molecular analyses. Primary SMCs were isolated from mouse (Adam17$^{f/f}$, Adam17$^{SMC}$) and human (±ADAM17 siRNA) thoracic aorta. SMCs were treated with elastase (0.4 U/ml, 5 min) and analyzed for various proteins. An ADAM17-selective inhibitor (PF-5480090, Pfizer) or vehicle was administrated to WT mice by oral gavage 3 days before and during the 14 days after TAA induction to evaluate the effect of pharmacological inhibition of ADAM17 on TAA formation and progression.

Results: ADAM17 protein levels were significantly increased in human TAAs, with the majority of ADAM17+ cells located in the medial and intimal layers. On day 14 after elastase treatment, Adam17$^{SMC}$ mice demonstrated smaller aortic dilation with less elastin fragmentation, SMC loss, and fibrillar collagen buildup compared to parallel Adam17$^{f/f}$ mice. However, similar inflammation (macrophages and neutrophils) and apoptosis (TUNEL) were observed in TAAs of both genotypes. Treatment with ADAM17-selective inhibitor significantly suppressed the formation and severity of TAA in WT mice. No gender-specific phenotype differences were observed. The elastase-induced increase in collagen I and III levels (mRNA and protein) was markedly suppressed in ADAM17-deficient TAA aortas and SMCs. Interestingly, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) levels were significantly increased in both mouse and human ADAM17-deficient VSMCs after elastase treatment, which was accompanied by attenuated TNFα and TGFβ1 signaling. The precise mechanisms by which ADAM17 regulates ECM synthesis or degradation still need further examination. However, our data so far suggest that the ADAM17-amphiregulin/connective tissue growth factor (CTGF)-epidermal growth factor receptor (EGFR)-fibroblast growth factor (FGF)-TGFβ1 signaling cascade may be the underlying mechanism for the destructive ECM remodeling in TAAs.

Conclusion: Cell specific ADAM17-deficient mice provided a valuable tool to determine the role of ADAM17 in TAA. Genetic and pharmacological inhibition of ADAM17 decrease formation and progression of TAA by regulating ECM remodeling, indicating that an ADAM17 selective inhibitor could serve as a potential therapeutic target for this devastating vascular disease.
PHARMACOLOGICAL TREATMENT OF PATIENTS WITH ANGINA WITH NO OBSTRUCTIVE CORONARY ARTERY DISEASE (ANOCA): A SYSTEMATIC REVIEW

Ricky Turgeon, Glen Pearson, Michelle Graham

**Background:** Fifty-one percent of women and 33% of men with angina and ischemia on provocative testing have angina with no obstructive coronary artery disease (ANOCA). These patients have impairments in quality of life that are comparable to individuals with obstructive CAD. Clinicians generally treat ANOCA with traditional anti-anginal agents, despite prior studies demonstrating variable response to these medications. Due to these disparities, we performed a systematic review to evaluate the efficacy and safety of available pharmacological therapies for ANOCA.

**Methods:** We systematically searched the Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and the World Health Organization International Clinical Trials Registry Platform from inception to February 2017 for randomized controlled trials (RCTs) evaluating any pharmacological therapy for ANOCA, excluding coronary spasm or slow flow phenomenon. The primary outcome of interest was quality of life. Secondary outcomes included other efficacy measures (functional class, angina frequency and severity, nitroglycerin use, exercise time and time to ST depression on treadmill), and safety outcomes (drug discontinuation and adverse events).

**Results:** We included 28 RCTs from 410 identified studies. All included trials had high or unclear risk of bias in at least one domain. Consistent evidence of subjective and objective efficacy demonstrated support for the use of beta-blockers, angiotensin convertase enzyme (ACE) inhibitors and statins. We found conflicting evidence of subjective benefit for calcium-channel blockers and ranolazine. One trial demonstrated the efficacy of nicorandil. Other interventions, most notably nitrates, did not significantly improve either subjective or objective efficacy outcomes. Table 1 summarizes the available evidence. Significant heterogeneity and incomplete outcome reporting precluded meta-analysis.

**Conclusion:** For patients with ANOCA, beta-blockers, ACE inhibitors and statins, either as monotherapy or in combination, demonstrated evidence for use as first-line agents for symptomatic angina relief. Clinicians may also consider calcium-channel blockers or ranolazine for patients with persistent symptoms despite first-line therapy; however, evidence for these interventions is less consistent.
Table 1. Summary of evidence for pharmacological therapy of angina with no obstructive coronary artery disease (ANOCA)

<table>
<thead>
<tr>
<th></th>
<th>Subjective improvement</th>
<th>Objective improvement</th>
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<tbody>
<tr>
<td><strong>Consistent evidence of benefit</strong></td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitors</td>
<td>Y (2)</td>
<td>Y (4)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Y (4)</td>
<td>Y (3)</td>
</tr>
<tr>
<td>Statins</td>
<td>Y (2)</td>
<td>Y (3)</td>
</tr>
<tr>
<td><strong>Conflicting or insufficient evidence of benefit</strong></td>
<td></td>
<td></td>
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<tr>
<td>Calcium-channel blockers</td>
<td>Conflicting (2+/1-)</td>
<td>Y (3)</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Insufficient (1+)</td>
<td>Insufficient (1+)</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Conflicting (3+/1-)</td>
<td>Insufficient (1+)</td>
</tr>
<tr>
<td><strong>No benefit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs</td>
<td>N (1)</td>
<td>?</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>N (1)</td>
<td>N (1)</td>
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<tr>
<td>Ivabradine</td>
<td>N (1)</td>
<td>N (1)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>N (3)</td>
<td>N (3)</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>N (1)</td>
<td>?</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>N (1)</td>
<td>N (1)</td>
</tr>
</tbody>
</table>

ACE: Angiotensin-converting enzyme, ARB: Angiotensin-II receptor blocker, N: No evidence of benefit, Y: Evidence of significant benefit, ?: Not assessed.

Numbers in brackets represent the number of supporting or negative trials.
IMPROVED OUTCOMES WITH NEGATIVE PRESSURE VENTILATION (NPV) DURING NORMOTHERMIC EX VIVO LUNG PERFUSION

Nader S. Aboelnazar, Sayed Himmat, Sanaz Hatami, Mohamad S. Burhani, Christopher W. White, Peter Dromparis, Michael Mengel, Darren H. Freed, Jayan Nagendran

**Background:** Normothermic Ex Vivo Lung Perfusion (EVLP) has increased the rate of donor organ utilization, and increased volumes of lung transplantation at centers that have adopted the technology. Current ventilation methodology for EVLP uses Positive Pressure Ventilation (PPV) with all clinically available devices. As ideal mimicry of native lung physiology would apply a negative pressure to the pleural surface of the lung (Negative Pressure Ventilation, NPV), we developed a novel ventilation system that replicates in vivo lung ventilation. We hypothesize that NPV would be superior to PPV during EVLP.

**Methods:** A fully automated NPV EVLP platform was developed and compared to conventional (PPV) EVLP. Pig and human lungs were perfused for 12 hours and physiologic parameters, cytokine profile, bullae and edema formation were analyzed. A total of 32 pig lungs were perfused, divided equally into 4 groups based on ventilation strategy and perfusate composition: acellular (STEEN solution™) and cellular (packed Red Blood Cells + STEEN solution™). Preliminary unutilized human lungs compared NPV-Cellular (N=3) and PPV-Cellular (N=3).

**Results:** Using a Student t test (mean±SE), pig and human lungs showed stable trends in lung oxygenation (>350 mmHg) and physiological parameters. Cytokine analysis of pig and human lungs showed significantly lower TNFα, IL-6, and IL-8 production with an NPV strategy regardless of perfusate (p<0.05). Moreover, there was a 42% reduction incidence of bullae with a NPV vs PPV strategy (Figure 1A, p=0.02). Porcine lung edema demonstrated lower weight gain with NPV, irrespective of perfusate (NPV-Cellular: 20.1 ± 4.1% vs PPV-Cellular: 39.0 ± 6.6%, Figure 1B, p<0.01; NPV-Acellular: 40.4 ± 5.3% vs PPV-Acellular: 88.1 ± 11.0%, Figure 1B, p<0.01). However, an acellular perfusate had greater edema formation, irrespective of ventilation strategy (Figure 1B, p<0.01). Interestingly, in human lungs a weight loss (“drying”) was observed (-8.0 ± 2.1% and 39.4 ± 5.6%, Figure 1C, p<0.01).

**Conclusion:** Negative pressure ventilation (NPV) has the potential to be more beneficial compared to the conventional positive pressure ventilation (PPV) with significantly less inflammation, bullae, and edema formation during extended EVLP for both perfusate groups. The value of a NPV strategy may lead to further improvements to currently available clinical EVLP platforms. Further studies are warranted on the value of NPV-EVLP in pre-clinical transplant models and clinical trials.
THE IMPACT OF PREHABILITATION ON FUNCTIONAL CAPACITY AND QUALITY OF LIFE FOR PATIENTS AWAITING CORONARY ARTERY BYPASS GRAFT SURGERY AND/OR MITRAL VALVE SURGERY

Andrea Joy Van Damme, Colleen Norris, David Buijs, Caroline Black, Kara Penney, Gabor Gyenes

Background: Evidence shows that patients’ functional capacity and psychosocial status deteriorate while waiting for coronary artery bypass graft (CABG) surgery. As such, prehabilitation (PREHAB) can play an important role in optimizing patients pre-operatively by improving aerobic capacity and minimizing anxiety. PREHAB has been linked to decreased lengths of stay (LOS) in hospital, reduced post-operative complications, and fewer readmissions. In order to examine the effect that PREHAB has on functional capacity (FC) and quality of life (QOL), the Northern Alberta Cardiac Rehabilitation Program (NACPR) has implemented a pilot program that looks specifically at these quality indicators and subsequent outcomes.

Methods: Stable patients waiting for scheduled CABG and/or mitral valve surgery are assessed both at baseline (prior to PREHAB) and then again during their fourth week in the program. FC is evaluated using a 6 Minute-Walk-Test (6MWT), and QOL is assessed using the Late Life Function and Disability Instrument (LLFDI), the EuroQOL Five Dimension Questionnaire (EQ-5D), and the Screening Tool for Psychosocial Distress (STOP-D). Baseline and 4 week data are collected and compared to evaluate whether PREHAB improves patients’ overall function and QOL. In addition, propensity matching is done using the APPROACH database to determine whether these improvements translate into differences in LOS and post-operative complications.

Results: Although data is preliminary, functional and QOL measures improved after 4 weeks in the program. Propensity matching (on 47 patients) demonstrated a trend suggesting fewer post-operative complications in the PREHAB group compared to no PREHAB [wound complications (p = 0.03)]. There was a statistically significant difference in CVICU LOS in the patients that incorporated exercise into their PREHAB program compared to those PREHAB patients that participated in counseling/education only [2.22 days vs 2.66 days respectively (p = 0.035)].

Conclusion: Preliminary descriptive data suggests an encouraging trend toward improved FC and QOL for patients in a PREHAB program. PREHAB has the potential to decrease post-operative complications; in addition, using exercise as a key modality may decrease in-hospital LOS.
THE CONTRIBUTION OF FATTY ACID AND KETONE BODY OXIDATION TO ENERGY PRODUCTION INCREASES IN THE FAILING HEART AND IS ASSOCIATED WITH A DECREASE IN CARDIAC EFFICIENCY

Kim Ho, Cory Wagg, Liyan Zhang, Jody Levasseur, Jason R.B. Dyck, John R. Ussher, Gary D. Lopaschuk

Background: The failing heart is energy-starved and inefficient due to perturbations in energy metabolism. Since recent evidence suggests that ketone body oxidation increases in the failing heart as an adaptive mechanism to counteract reductions in fatty acid oxidation, our aim was to assess overall cardiac metabolism in heart failure, to establish what metabolic alterations contribute to reduced cardiac efficiency.

Methods: C57BL/6J male mice (12 wk old) underwent either sham surgery, or transverse aortic constriction (TAC) surgery to induce pressure overload hypertrophy over a 4 wk period. Isolated working hearts from these mice were then perfused with appropriately ³H or ¹⁴C labelled glucose (5 mM), palmitate (0.8 mM), and β-hydroxybutyrate (0.6 mM) to assess oxidative metabolism and glycolysis.

Results: A 45% reduction in %EF was seen in intact TAC mice and a 54% decrease in cardiac work was seen in isolated working hearts from TAC mice. However, normal cardiac Krebs Cycle acetyl CoA production was seen compared to sham mice, reflecting a reduction in cardiac efficiency. Correspondingly, absolute glucose oxidation rates decreased in TAC compared to sham hearts, whereas absolute rates of fatty acid and ketone body oxidation were similar. However, normalization to cardiac work revealed that glucose oxidation was not depressed in failing hearts, although glycolysis was increased. Conversely, both fatty acid and ketone body oxidation increased in TAC hearts when normalized to cardiac work. This increased reliance on fatty acid oxidation challenges the current dogma suggesting that fatty acid oxidation is depressed in the failing heart.

Conclusion: In the failing heart, a decreased cardiac efficiency is associated with increases in the contributions of ketone body and fatty acid oxidation to energy production. The latter observation suggests that normalizing excessive fatty acid oxidation in the failing heart may be a novel approach to improve cardiac efficiency.
DETERIORATION OF FUNCTIONAL ABILITIES IN CHILDREN SURVIVING THE FONTAN OPERATION

M. Florencia Ricci, Billie-Jean Martin, Ari Joffe, Gwen Bond, Irina Dinu, Gonzalo Garcia Guerra, Charlene Robertson

Background: Deficits in functional abilities significantly impact the ability of a child to function independently in life. We hypothesized that deterioration in functional abilities (DFA) is not uncommon after the Fontan operation, and that stroke is often the event leading to DFA. Our objectives were to determine: 1) the frequency of DFA post-Fontan; 2) the frequency of peri-Fontan stroke among those with and without DFA; 3) any potentially modifiable acute care predictors that may lead to a reduction of DFA.

Methods: From 1996-2016, 192 children prospectively registered in The Western Canadian Complex Pediatric Therapies Follow-up Program underwent a Fontan operation at Stollery Children’s Hospital. Children who underwent a Norwood BT as their first palliative surgery and those who died, refused or were lost to follow-up were excluded. At age 2 (pre-Fontan) and 4.5 years (post-Fontan), children received multidisciplinary assessment; the Adaptive Behavior Assessment System-II general adaptive composite (GAC)(population mean: 100, SD:15) was determined. DFA was defined as a 1SD decrease in GAC from pre- to post-Fontan scores. Stroke diagnosis was confirmed through retrospective chart review. Predictors of DFA were analyzed using multiple logistic regression analysis.

Results: Post-Fontan, DFA occurred in 34/133 (25.6%) of assessed survivors. Overall mean GAC was 90.6 (SD 17.5) at 2 years and 88.3 (19.2) at 4.5 years. In those with DFA, mean GAC at 2 years was 96.2(17.5) vs. 74.5(16.6) at 4.5 years. Evidence of peri-Fontan stroke was found in 18/133(13.5%), in 10/34(29.4%) of children with DFA vs. 8/99(8.1%) of children without DFA (p=0.002). Mean post-Fontan GAC in children with stroke was 76.9(21) compared to 90.1(18.3) among those without stroke (p=0.01). Independent predictors of DFA are: peri-Fontan stroke, Odds Ratio (OR) 5 (95%CI:1.74, 14.36 ) (p=0.003), and age at Fontan (years), OR 1.67 (95%CI 1.02, 2.73) (p=0.04).

Conclusions: It is important to assess the longitudinal trajectory of functional abilities in children undergoing single ventricle palliation, as more than 25% of surviving children show DFA. Efforts to prevent peri-Fontan stroke and perhaps complete the Fontan operation at an earlier age may lead to a reduction in the frequency of DFA.
DIFFERENTIAL REGULATION OF P53 BY PYRUVATE KINASE M2 CAN BE THERAPEUTICALLY TARGETED IN CHEMOTHERAPY-INDUCED CARDIOTOXICITY

Bruno Saleme, Vikram Gurtu, Adam Kinnaird, Aristeidis Boukouris, Corey Wagg, Gary D. Lopaschuk, Gopinath Sutendra

**Background:** Chemotherapy-induced cardiotoxicity (CIC) is a common clinical problem as many chemotherapeutics induce the pro-apoptotic transcription factor p53 in the tumour and nonspecifically in the heart, promoting heart failure. Although inhibition of p53 shows benefit in heart failure models, it would not be a valid approach for CIC, as it would prevent p53-mediated tumour regression. Targeting potential regulators of p53 that would have an opposing role on p53-transcriptional activity and apoptosis in the heart compared to the tumour would be ideal. An intriguing difference between the heart and tumor microenvironments is the partial pressure of oxygen with the former being high and the latter low, suggesting that redox-sensitive proteins could provide therapeutic targets against CIC. We hypothesized that stabilization of the redox-sensitive pyruvate kinase M2 (PKM2; which was previously shown to interact with and regulate nuclear transcription factors) can differentially regulate p53-transcriptional activity and apoptosis between the heart and tumour, preventing CIC.

**Methods:** p53 was induced via Nutlin/Adriamycin. Cell lines: A549. Reagents: ß-lapachone (oxidizing agent), TEPP-46 (stabilizes dimer pKM2), TUNEL. Techniques: Immunoblot, qRT-PCR, co-immunoprecipitation (co-IP), CRISPR, site-directed mutagenesis, mass-spectrometry (MS), echocardiography.

**Results:** Co-IP shows that p53 and PKM2 can directly interact. CRISPR-generated PKM2 knockout cells have increased p53-transcriptional activity (assessed by p21/PUMA) compared to wild-type. Stabilization of dimer PKM2 (with TEPP-46) when cysteine-423 (identified by MS and site-directed mutagenesis) is oxidized or reduced results in inhibited or enhanced p53-transcriptional activity and apoptosis (TUNEL), respectively. In-vivo, cysteine-423 is preferentially oxidized in the heart compared to the tumour of xenotransplanted mice with lung or mammary tumours, and stabilization of PKM2 with TEPP-46 completely prevented chemotherapy (Adriamycin)-induced apoptosis and heart failure (via Echocardiography), but additively enhanced chemotherapy-mediated tumor apoptosis and tumour regression (Figure).

**Conclusion:** The novel interaction and differential regulation of p53-transcriptional activity and apoptosis by PKM2 could provide the basis for novel therapeutic strategies against CIC.
Figure: Therapeutically stabilizing PKM2 with TEPP-46 inhibits p53 transcription activity and apoptosis in the heart, while enhancing p53 activity and apoptosis in the tumor.

A. PKM2 stabilization via TEPP-46 prevents Adriamycin-mediated apoptosis in the heart (measured by TUNEL staining in green, nuclear stain DAPI in blue) while further enhancing apoptosis in the tumor of xeno-transplanted mice with human lung cancer (n=5 mice/group, * denotes p<0.05 vs control, # denotes p<0.05 vs Adriamycin).

B. Cysteine-423 of PKM2 is preferentially oxidized in the heart compared to the tumor. Stabilization of dimer PKM2 with TEPP-46 results in inhibition of p53 transcriptional activity and apoptosis in the heart preserving cardiac function while enhancing p53 transcriptional activity in the tumor enhancing tumor regression.
IDENTIFYING LOW-RISK PATIENTS FOR EARLY DISCHARGE FROM EMERGENCY DEPARTMENT WITHOUT USING SUBJECTIVE DESCRIPTIONS OF CHEST PAIN

Nariman Sepehrvand, Yinggan Zheng, Paul W. Armstrong, Robert Welsh, Justin A. Ezekowitz

**Background:** Several accelerated diagnostic protocols (ADP) have been developed to allow emergency department (ED) physicians to identify which patients are appropriate for early discharge after presentation with chest pain. Most ADPs modify the algorithm based on the subjective chest pain characteristics.

**Purpose:** We investigated the performance of 3 established major ADPs, simplified by eliminating the need for chest pain as a descriptor.

**Methods:** We pooled patients from PROACT-3 and 4 trials, which enrolled patients presenting via ambulance with chest pain or dyspnea. The simplified Vancouver Chest Pain Rule (sVCPR), the simplified Emergency Department Assessment of Chest Pain Score (sEDACS) ADP and the ADAPT-ADP were compared using the sensitivity, specificity, and positive and negative predictive values (NPV). The primary outcome was the diagnosis of acute coronary syndrome (ACS); 30-day cardiac events were also explored.

**Results:** 1081 patients were included (median age 67 years, 53% male, median GRACE score 113) of which, 222 ACS diagnosis and 150 cardiac events occurred within 30 days after index ED presentation. The sVCPR, sEDACS and ADAPT-ADP, respectively, identified 9.7%, 13.3% and 4.1% of patients as low risk with a NPV of 98.1%, 95.8% and 93.3%. For 30-day cardiac events, all 3 scores had 100% NPV and 100% sensitivity.

**Conclusion:** The diagnostic protocols performed well without their chest pain component. Further studies are suggested to explore the performance of ADPs combined with high-sensitive troponin assays in order to facilitate rapid appropriate identification of low-risk patients.
Table: Operating characteristics of the different rules

<table>
<thead>
<tr>
<th></th>
<th>sVCPR</th>
<th>sEDACS-ADP≥3</th>
<th>ADAPT-ADP</th>
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<tr>
<td>Primary outcome of ACS diagnosis within 30 days</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>99.1 (96.8, 99.9)</td>
<td>97.3 (94.2-99.0)</td>
<td>98.7 (96.1-99.7)</td>
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<tr>
<td>Specificity</td>
<td>12.0 (9.9, 14.3)</td>
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<td>PPV</td>
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<tr>
<td>NPV</td>
<td>98.1 (93.3, 99.7)</td>
<td>95.8 (91.2-98.5)</td>
<td>93.3 (81.7-98.6)</td>
</tr>
<tr>
<td>Secondary outcome of 30-day cardiac events</td>
<td></td>
<td></td>
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<tr>
<td>Sensitivity</td>
<td>100 (97.6, 100)</td>
<td>100 (97.5, 100)</td>
<td>100 (97.6, 100)</td>
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<tr>
<td>Specificity</td>
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<td>15.4 (13.2, 17.9)</td>
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<tr>
<td>PPV</td>
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<td>16.0 (13.7, 18.5)</td>
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<tr>
<td>NPV</td>
<td>100 (96.6, 100)</td>
<td>100 (97.4, 100)</td>
<td>100 (92.1, 100)</td>
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<td>Identified as low risk, %</td>
<td>9.7</td>
<td>13.3</td>
<td>4.1</td>
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ACS: Acute Coronary Syndrome; ADAPT: Accelerated Diagnostic protocol to Assess Patients with chest pain using contemporary Troponins as the only biomarker; ADP: Accelerated Diagnostic Protocol; NPV: negative predictive value; PPV: positive predictive value; sEDACS: the simplified emergency department assessment of chest pain score; sVCPR: simplified Vancouver Chest Pain Rule.
BASIC SCIENCE POSTERS
Background: Cardiac fatty acid oxidation in the newborn dramatically increases shortly after birth, while glucose oxidation remains low until weaning. In newborn rabbit hearts, volume overload hypertrophy delays this increase in fatty acid oxidation, while keeping glucose oxidation low. This results in a decreased capacity to produce energy in the heart and increases the susceptibility to ischemic injury. The presence of cardiac hypertrophy in patients with congenital heart defects also decreases the maturation of fatty acid oxidation, but it is not clear what happens to glucose oxidation. We therefore determined what happens to the control of glucose oxidation in hypertrophied human newborn hearts.

Methods: Human right ventricular biopsy samples were collected during corrective heart surgery from neonates aged 101-200 days (an age group with increased fatty acid oxidation enzyme activity compared to 0-100 day old hearts). Samples were grouped based on the presence or absence of right ventricular hypertrophy, as assessed by echocardiography. The heart tissues were processed for Western blot analysis.

Results: Pyruvate dehydrogenase (PDH), the rate-limiting enzyme of glucose oxidation, had significantly increased phosphorylation in hypertrophied vs. non-hypertrophied hearts (1.08±0.09 vs. 0.81±0.06 arbitrary units, respectively, n=6, p<0.05), resulting in inactivation of PDH. Concomitantly, expression of the PDH kinases, PDK2 and PDK4, were significantly increased in hypertrophied hearts. Transcription factors PPARα and ERRα, which are known to regulate PDH kinases, showed no changes between groups, while E2F1, a transcriptional regulator of PDK2 and PDK4, was increased. Components of the E2F1 pathway were also upregulated in the hypertrophied group, namely P-cyclin D1 and CDK4.

Conclusion: Hypertrophy of the newborn heart upregulates E2F1-mediated transcription of PDH kinases, thereby phosphorylating and inhibiting PDH and reducing glucose oxidation rates. This may contribute to compromised energetics in the newborn heart.
INCREASED AORTIC STIFFNESS FOLLOWING EXPOSURE TO CHRONIC HYPOXIA IN RATS

Victor Do, Praveen Kumar, Amin Shah, Jude Morton, Sandra Davidge, Jesus Serrano-Lomelin, Lisa K Hornberger

**Background:** It has been previously demonstrated in rats that fetal hypoxia, a consequence of intrauterine growth restriction (IUGR), is associated with altered left ventricular (LV) diastolic function beginning in early postnatal life (2 weeks). The aims of this study were to determine if intrauterine exposure to hypoxia results in increased aortic stiffness, if these changes persist longitudinally and if there are correlations between aortic stiffness and other systolic and diastolic function parameters. We hypothesized that intrauterine hypoxia exposure alters aortic stiffness which may contribute to the evolution of myocardial dysfunction after birth.

**Methods:** Six pregnant rats were exposed to hypoxic conditions (11.5% FiO2) from E15-21 and 3 were maintained in normoxic conditions. After delivery, 4 neonatal rats from each group were examined longitudinally at day 1, 3, and weeks 1, 2, 4, 8 for changes in aortic stiffness. Aortic stiffness was assessed by measuring the pulse wave velocity (PWV) in the ascending aorta at 3 points: 1. Proximal to the branch of the first brachiocephalic artery, 2: at the level of the diaphragm and, 3: just above the aortic bifurcation into the iliac arteries. T1 was the time interval from the peak of the R wave by ECG to onset of flow in the ascending aorta and T2 from peak of the R wave to onset of flow in either the mid aorta or distal aorta. The distance from the suprasternal notch to the subxiphoid process and to the anterior superior iliac spine was measured in each animal. The PWV was calculated using: [distance / (T2-T1)]. Three consecutive tracings were assessed.

**Results:** Aortic stiffness was significantly increased in rats exposed to a hypoxic intrauterine environment (P<0.0001). This change persists longitudinally at all time points including at week 8 and was at both the diaphragm and aortic bifurcation regions. The difference between the two groups decreases over time, at week one PWV (m/s) is 2.4 +/- 1 vs 11 +/- 9.2, compared to at 8 weeks when the 3.7 +/- 0.6 vs 5.3 +/- 1.0. There were no significant differences between male and female rats or individual pregnancies.

**Conclusion:** Prenatal exposure to hypoxia was associated with increased aortic stiffness during early development. Further studies will explore whether aortic stiffness continues to be increased in later stages of life, whether this is associated with other myocardial and vascular diseases and the molecular pathways involved in the adaptation to hypoxic insult.
WORSENING OF CARDIAC FUNCTION IS PREVENTED BY EMPAGLIFLOZIN MICE WITH HEART FAILURE

Nicole J Byrne, Nirmal Parajuli, Jody Levasseur, Jamie Boisvenue, Grant Masson, Donna Beker, Jason RB Dyck

Background: Recent work has shown that the anti-diabetes drug empagliflozin, a inhibitor of the renal-SGLT2 transporter, reduced hospitalization for heart failure (HF) and reduced cardiovascular-related deaths in patients with type 2 diabetes. Since the SGLT2 receptor does not exist in cardiac tissue, the mechanisms responsible for cardioprotective actions of empagliflozin are currently unknown. In the present study, we used a mouse model of pressure-overload induced HF to investigate whether empagliflozin improves HF outcomes in mice without concurrent diabetes.

Methods: 8-week old, male C57Bl/6 mice were subjected to either sham or transverse aortic constriction (TAC) surgery to induce HF. Two to 3 weeks following surgery, mice with established HF (% ejection fraction (%EF) <45) were administered either vehicle or empagliflozin (10 mg/kg/day) by oral gavage daily for 2 weeks.

Results: While vehicle-treated HF mice experienced a progressive worsening of cardiac function (%EF reduced from 33% to 24%) over the 2 week treatment period, this decline was blunted in empagliflozin-treated HF mice (%EF maintained at 35%). Despite improving systolic function, empagliflozin did not improve cardiac remodeling or diastolic function in mice with HF when compared with vehicle-treated mice. Interestingly, isolated hearts from HF mice treated with empagliflozin displayed significantly improved ex vivo cardiac output and cardiac work compared to vehicle-treated controls, suggesting that the ability of empagliflozin to prevent worsening cardiac function in mice with HF was an intrinsic cardiac effect and not based on potential hemodynamic changes. This improved ex vivo function was also associated with increased myocardial fatty acid oxidation rates, suggesting improved energetics in hearts from empagliflozin-treated HF mice compared to controls.

Conclusion: Empagliflozin treatment of mice with established HF blunts the decline in cardiac function both in vivo and ex vivo demonstrating that empagliflozin can influence cardiac function even in the absence of hemodynamic changes. We also provide evidence that empagliflozin improves myocardial energetics in failing hearts and suggest that this contributes to improved systolic function. As such, the data provided herein suggest that empagliflozin may be useful for the treatment of patients with HF even in the absence of diabetes.
CHF-BAS-2

R/S ENANTIOMERS OF 19-HYDROXYEICOSATETRAENOIC ACID COULD BE PROMISING THERAPEUTIC TARGETS IN CARDIAC HYPERTROPHY AND HEART FAILURE


Background: Progress made over the past decades in a multitude of disciplines upholds an evident role for cytochrome P450 (CYP) enzymes and their arachidonic acid (AA) metabolites in cardiac physiology and wide array of cardiac diseases. In the heart, CYP enzymes catalyze the formation of R/S enantiomers of 19-hydroxyeicosatetraenoic acid (19-HETE) via subterminal hydroxylation reaction of AA. We have recently shown that the racemic (±)19-HETE provides cardioprotection against angiotensin II-induced cardiac hypertrophy, however, the differential biological effects of R/S enantiomers yet to be investigated. Therefore, the objective of the current study is to characterize the biological roles of R and S enantiomers in human ventricular cardiomyocyte RL-14 cells.

Methods: Human ventricular cardiomyocyte RL-14 cells were treated with vehicle or 20 μM of 19(R)-HETE or 19(S)-HETE in serum-free media for 24 h. The levels of mid-chain HETEs, terminal/subterminal HETEs and epoxyeicosatrienoic acid (EETs) were determined using liquid chromatography-electron spray ionization-mass spectrometry (LC/MS). The level of gene expression was characterized using real-time PCR. Thereafter, Western blot analysis was performed to assess the protein levels of different enzymes.

Results: The targeted metabolomic analysis showed that both (R)- and (S)-19-HETE significantly decreased the metabolite formation rate of mid-chain HETEs namely 15-, 12-, 8- and 9-HETE compared to the control group while the level of 5-HETE was significantly decreased solely by the S-enantiomer. The levels of 11-HETE, terminal/subterminal HETEs and EETs were not significantly changed compared to the control group. Gene expression and Western blot analysis showed that the decrease in mid-chain HETEs levels was attributed to the decrease in the protein expression levels of 5- and 12-lipoxygenase (LOX) mediated by both enantiomers while the level of 15-LOX was only decreased by 19(S)-HETE. Moreover, both enantiomers significantly decreased the level of cyclooxygenase-2 (COX-2). CYP enzymes were not significantly affected at the gene and protein levels.

Conclusion: Our findings provide the first demonstration that both R- and S-enantiomers of 19-HETE significantly decreased the levels of mid-chain HETEs via LOX enzymes- and COX-2-dependent mechanisms. Our data suggest that both R/S enantiomers of 19-HETE could serve as promising therapeutic targets in cardiac hypertrophy and heart failure.
ENDOPLASMIC RETICULUM STRESS IN EX VIVO HEART PERFUSION:
A COMPARISON BETWEEN WORKING VERSUS NON-WORKING MODES
Sanaz Hatami, Xiao Qi, Christopher W. White, Mohamad Burhani, Nader Aboelnazer,
Sayed Himmat, Allan Wu, Nobutoshi Matsumura, Martin Ondrus, Jayan Nagendran,
Darren H. Freed

Background: Ex vivo heart perfusion (EVHP) provides the opportunity to preserve the
donated heart in a semi-physiologic beating status, to monitor function and potentially
improve the quality of marginal/declined hearts. Currently, the clinically available EVHP
apparatus supports the heart in non-working mode (NWM). EVHP in working mode (WM)
however, may be better in terms of function assessment and preservation. Endoplasmic
reticulum (ER) is an organelle of particular importance for cardiac function. In response to
different stresses and pathophysiologic stimuli, the unfolded protein responses (UPR) can be
activated, which if severe/prolonged, can lead to functional decline/cardiac failure. The aim
of the present study was to investigate the ER stress responses in the EVHP setting and to
compare it in the working vs non-working modes.

Methods: 19 female domestic breed pigs (37-47 kg) were included. The procured hearts
were immediately mounted on a custom EVHP apparatus and perfused for 12 hours. In
NWM group (n=6), perfusion continued in non-working mode with no left atrial flow, whereas
the heart perfused with a left atrial pressure of 6 mmHg from the first hour until the end of
perfusion in WM (n=9). Cardiac function parameters were compared between two groups. At
the end of perfusion, left ventricle (LV) tissue specimens were collected and analyzed for ER
stress markers using protein immunoblotting method. The results were compared between
two groups and with baseline EVHP samples (n=4, in vivo and T0).

Results: In both groups, cardiac function declined overtime but the function parameters
were better preserved in working mode group (e.g. cardiac index, P<0.01). Downstream
effectors of activated PKR-like ER kinase (PERK) (e.g. eIF-2α) were enhanced at the end
of EVHP (p<0.05) compared to baseline, with no difference between two groups (p>0.05).
Inositol-requiring protein 1 (IRE1) and activating transcription factor-6 (ATF-6) pathway
markers were significantly higher in perfusion baseline (T0= 15 minutes of perfusion; p<0.05)
with no significant difference in WM versus NWM at the end of perfusion.

Conclusion: The enhanced UPR during EVHP, was not associated with ventricular load and
perfusion mode. Different branches of ER stress might be activated in early and later phases
of EVHP. To optimise the EVHP protocols for the aim of better cardiac function preservation
and recovery, further studies are warranted to clarify the causes of ER stress during EVHP
and its related consequences.
In vivo → Peri-procurement stress → T0 → EVHP → T12

Endoplasmic reticulum

PERK pathway

IRE-1α
p-IRE-1α

eIF-2α
p-eIF-2α

ATF-6

Nucleus

CHOP

Graph showing expression levels of various proteins under different conditions.
ASSESSMENT OF PRELOAD-RECRUITABLE STROKE WORK DURING BIVENTRICULAR EX VIVO HEART PERFUSION: A NOVEL APPROACH ELIMINATING THE PRESSURE-VOLUME LOOP CATHETER

Christopher W White, Jayan Nagendran, Darren H Freed

**Background:** Ex vivo heart perfusion may facilitate resuscitation of non-utilized donor hearts. A reliable means of demonstrating organ viability prior to transplantation is required. Preload recruitable stroke work (PRSW) is a load independent metric of myocardial function obtained using a pressure-volume loop catheter; however, the expensive, cumbersome, and invasive nature of the equipment limits clinical translation. We sought to develop a non-invasive method of measuring PRSW in an ex vivo, bi-ventricular, working heart device.

**Methods:** A bi-ventricular working heart device was developed, and a computer program was written for control and integration of pressure (left atrial, right atrial, aortic, and pulmonary arterial) and flow (left atrial, and right atrial) data. The hearts of 40 kg pigs were procured, perfused with a blood-STEEN solution, and transitioned into a working mode by increasing the revolutions per minute on the preload pump. The partial occlusion clamp was adjusted to ensure right atrial flow did not exceed left atrial flow. Stroke volume was calculated as follows: stroke volume (mL/beat) = atrial flow (mL/min) / heart rate (beats/min). Stroke work was calculated as follows: stroke work (mmHg*mL) = \[\text{mean arterial pressure - atrial pressure}\] x stroke volume (mL).

**Results:** Stroke work was measured during a computer-controlled reduction in revolutions per minute on the preload centrifugal pump, producing a linear reduction in atrial pressure. PRSW was determined by calculating the linear regression of stroke work and atrial pressure.

**Conclusion:** PRSW can be measured in a non-invasive fashion during ex vivo heart perfusion in a biventricular-working mode, without the need for pressure-volume loop catheters. This method of myocardial functional assessment may aid in selecting viable donor hearts for transplantation in the future.
INTRACELLULAR LOCALIZATION OF MMP-2 IN DOXORUBICIN-TREATED CARDIOMYOCYTES

Nils Moser, Brandon Chan, Andrej Roczkowsky, Mathieu Poirier, Ramses Ilarraza, Richard Schulz

Background: The anthracycline class of anticancer drugs is commonly used to treat a variety of solid tumor and hematological cancers. Despite their effectiveness, anthracyclines, including doxorubicin (DXR), can cause heart failure in up to 9% of cancer patients. Current strategies to minimize heart injury are limited to restricting the lifetime cumulative dose, which compromises anticancer therapy and patient outcome. In order to develop an effective adjuvant therapy, we need to better understand the cardiotoxic mechanism of DXR. Current hypotheses for DXR cardiotoxicity include myofibrilysis and increased oxidative stress in the heart. Oxidative stress can activate matrix metalloproteinase-2 (MMP-2), an intra- and extracellular protease implicated in numerous cardiac pathologies. Once active, MMP-2 cleaves various intracellular proteins including troponin I and alpha-actinin, impairing cardiac contractile function. In addition to the sarcomere, MMP-2 has been localized to other subcellular locales including the nucleus, mitochondria, the mitochondria-associated membrane, and caveolae. We investigated the pathophysiological role of MMP-2 by determining its subcellular localization in DXR-treated neonatal cardiomyocytes. We hypothesized that DXR would increase the level and/or subcellular localization of MMP-2 to the sarcomere and disrupt its structure.

Methods: Neonatal rat ventricular myocytes (NRVM) from 1-2 day old rat pups were treated with DXR (0.5 µM) for 24 hours. MMP-2 protein levels and activity in cell lysates were determined by western blot and gelatin zymography, respectively. To determine the sarcomeric localization of MMP-2, cells were fixed and labeled with fluorescein-conjugated antibodies for MMP-2, troponin I, and alpha-actinin and visualization was done using a Leica SP5 laser scanning confocal microscope.

Results: MMP-2 protein levels and enzymatic activity were increased in NRVM lysates following 24 hour DXR treatment. DXR-treated NRVM showed increased intracellular MMP-2 fluorescence with a filamentous redistribution compared to control cells. Troponin I staining showed a thinning of the sarcomeric structure within the cytoplasm of NRVM following DXR treatment. DXR caused increased MMP-2 colocalization with troponin I.

Conclusion: Intracellular MMP-2 fluorescence was increased and redistributed following 24-hour DXR treatment in NRVM. Troponin I rearrangement suggests myofibrilysis may play a role in contractile dysfunction caused by DXR cardiotoxicity. A better understanding of DXR-induced heart injury could lead to the development of an effective inhibitor of MMP-2 as an adjuvant therapy.
CHF-BAS-6

ADIPONECTIN GENE THERAPY ON EX VIVO LUNG PERFUSION TO IMPROVE LUNG TRANSPLANTATION OUTCOME

Sayed Himmat, Nader Aboalnazar, Mohamad Burhani, Nobutoshi Matsumura, Sanaz Hatami, Jody Levasseur, Amy Barr, Jason Dyck, Darren H. Freed, Jayan Nagendran

Background: A growing body of evidence highlights normothermic ex-vivo lung perfusion as a valuable platform for the delivery of therapeutic agents to donor lungs while evaluating them prior to transplantation. Progression of in-vivo gene therapy faces anchoring heralds from fatalities in early trials. Adiponectin, a bioactive peptide, has significant anti-inflammatory and cytoprotective properties to the pulmonary vascular endothelium and airway epithelium. In addition, low levels of plasma adiponectin increase the susceptibility of the lung to inflammatory related injury.

Methods: Procured lungs from nine Yorkshire domestic pigs (35-45kg) are randomly assigned to three treatment groups, where lungs are perfused on EVLP for 12 hours: 1) Ad-mCherry: with adenovirus-mCherry in the perfusate, 2) Ad-ApN Gene Therapy: adenovirus-adiponectin group, and 3) EVLP-Control. Baseline physiological data and cytokine profile are assessed in the EVLP-control group. Ad-mCherry, facilitates the visualization of viral distribution using florescence overlay pictures. In addition, levels of expressed adiponectin over 12 hours, will be measured in Ad-ApN perfused lungs using immunoassays and tissue western blots.

Results: Thus far, perfusion of control lungs (n=6) showed stable physiologic parameters over 12 hours. Lung dynamic compliance (Cdyn) remained stable from 16.4 ± 2.6 ml/cm H2O (T1) to 25.6 ± 2.5 ml/cm H2O (T11). There was a trend towards improved pulmonary vascular resistance (PVR) from 609 ± 78 dyn-s/cm5 to 423 ± 53 dyn-s/cm5, (p = 0.055). Weight gain was 60% on average. Moreover, analysis of pro-inflammatory cytokines in perfusate samples taken every two hours, showed a significant increase in TNFα, IL-6 and IL-8. More importantly, Ad-mCherry perfused lungs showed increased florescence in all lobes compared to controls, on pictures taken at T12.

Conclusion: Our results so far showed feasibility of intravascular delivery of adenoviral gene therapy using EVLP. We expect to show evidence of reduced inflammatory markers and improved function of adiponectin transduced lungs. Moreover, measure an increase in adiponectin expression in the perfusate over time from respective lungs. Finally, using transplant models to demonstrate pre-clinical safety and efficacy of ex-vivo Ad-ApN gene therapy.
VARIABLE EXPRESSIONS OF PRO-FIBROTIC MARKERS OBSERVED IN PRIMARY HUMAN MESENCHYMAL CELLS SEEDED IN DECELLULARIZED HUMAN CARDIAC EXTRACELLULAR MATRIX

Alison L. Müller, Yilun Wu, Kayla Knol, Darren H. Freed

**Background:** The rise of biomedical engineering working has contributed significantly to the tissue engineering research field; however, more physiologically relevant scaffolds are necessary in order to study endogenous progenitor cell differentiation to optimize research outcomes. Our lab has a keen interest in pathological fibrosis occurring in cardiovascular disease where cells from the bone marrow as well as circulating and resident fibroblasts, differentiate into a pro-fibrotic phenotype that contributes to scar formation. This often leads to heart failure and is a significant barrier in developing effective cell therapy techniques that could regenerate cardiac muscle. It is not clearly understand which specific factors influence endogenous mesenchymal cells to become pro-fibrotic; however, we have recently optimized permits study comparing healthy and pro-fibrotic extracellular matrix tissue. This allows us to better understand, and therefore potentially inhibit, the molecular mechanisms causing endogenous pro-fibrotic mesenchymal cell differentiation that could complement cell therapies, not just for regenerating cardiac tissue, but also other tissues afflicted by pathological fibrosis

**Methods:** Human ventricular tissue from explanted (EH) and un-utilized donor hearts (CH) were sliced between 100-200 μm and subject to a decellularization process occurring over four days. After decellularization, the extracellular matrix slices were co-incubated with primary human atrial fibroblasts (hAFs) or bone-marrow derived mesenchymal progenitor cells (hMPCs). Recellularized samples were homogenized followed by RNA isolation. qRT-PCR was performed to quantify mRNA levels of pro-fibrotic markers including collagen1α1 (Col1α1), collagen 1α2 (Col1α2), myosin heavy chain-9 (MYH9), and myosin heavy chain-10 (MYH10). Scanning electron microscopy (SEM) was performed to visualize the difference between decellularized and recellularized tissues.

**Results:** SEM showed a lack of cells on decellularized tissue, but a presence of cells on recellularized tissues. Analysis of pro-fibrotic mRNA expression determined both hAFs and hMPCs exhibited an increase in expression in EH compared to CH hearts. There was also a significant increase in Col1A1 expression when comparing recellularized tissue to traditional growth on plastic culture dishes.

**Conclusion:** The ability to reseed decellularized human ventricular extracellular matrix in both human explanted and un-utilized donor hearts can be used to compare differences among cell types and their responses between healthy and damaged or diseased cardiac ECM among different hearts and even within the same heart. This has implications for stem cell therapies targeting tissue regeneration in pro-fibrotic environments, where additional measures may need to be implemented in order to prevent the ECM environment from influencing unfavourable pro-fibrotic differentiation.
CHF-BAS-8
DYNAMIC NETWORK OF ANGIOTENSIN PEPTIDES IN HEART FAILURE:
ROLE OF ANGIOTENSIN 1-7 AND RECOMBINANT HUMAN ACE 2
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Background: Heart failure (HF) patients represent a vulnerable patient population with unacceptably high morbidity and mortality. The renin-angiotensin system (RAS) is activated in heart failure (HF) and inhibition of RAS is mainstay therapy for HF. Angiotensin converting enzyme 2 (ACE2) and its product, angiotensin 1-7, are important negative regulators of the RAS.

Methods: Using prospective cohorts with chronic (n=42) and acute (n=42) HF, quantification of sequential cleaved products of Angiotensin I (Ang 1-10) was performed in plasma (harvested and stored at -80°C) using a unique LC-MS technique. Angiotensin II (Ang II) metabolism was examined in human explanted hearts with dilated cardiomyopathy (n=25).

Results: The dynamic range of the RAS was large with maximal equilibrated peptide levels 8-10 fold greater than baseline circulating levels. In chronic HF patients receiving ACE inhibition, plasma Ang II was suppressed and plasma Ang 1-7 was elevated while acute HF and patients receiving angiotensin receptor blocker had higher plasma Ang II with lower Ang 1-7 levels. Suppressed Ang 1-7/Ang II ratio was associated with worsening HF symptoms and longer hospitalization. Recombinant human ACE2 effectively metabolized Ang 1-10 and Ang II into Ang 1-9 and Ang 1-7, respectively. Myocardial Ang II levels in explanted human hearts with dilated cardiomyopathy were elevated despite ACE inhibition with elevated chymase activity and levels and, Ang II was effectively converted to Ang 1-7 by rhACE2.

Conclusion: Plasma angiotensin peptides represents a dynamic network which is altered in HF and in response to rhACE2. Increased plasma Ang 1-7 level is linked to ACE inhibitor use while acute HF reduces plasma Ang 1-7 levels and suppressed Ang 1-7/Ang II ratio. Increased chymase activity elevates Ang II levels in failing explanted human hearts. rhACE2 effectively normalized elevated AngII while increasing Ang1-7 and Ang1-9 levels.
EXTRACELLULAR MATRIX BIOMATERIAL PROMOTES CARDIAC REPAIR THROUGH AN ACTIVE BIO-INDUCTIVE FIBROBLAST GROWTH FACTOR-2 DEPENDENT MECHANISM

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Background: We previously demonstrated that epicardial application of extracellular matrix (ECM) biomaterial prevents LV remodeling and improves functional recovery following myocardial infarction (MI). In this study we aim to determine if the underlying mechanism of benefit is a consequence of the bio-inductive properties of the ECM biomaterial. We hypothesize that ECM biomaterial will promote functional recovery after ischemic injury by stimulating vasculogenesis through a bio-inductive effect.

Methods: Biologically active ECM biomaterial (CorMatrix-ECM) was compared to ECM biomaterial inactivated by chemical treatments. The paracrine response of human cardiac fibroblasts (N=6) to ECM biomaterial was characterized in vitro. In vivo active (N=16) or inactive (N=16) ECM biomaterial was surgically applied to the infarcted myocardium following coronary artery ligation in a rat model. Indices of cardiac performance were quantified by pressure volume loop analysis 14 weeks post-MI.

Results: Human cardiac fibroblast treated with active ECM biomaterial demonstrated increased vasculogenic growth factor production compared to inactive ECM biomaterial treated cells (FGF-2: 7.09±4.05 vs. 2.63±1.40 fold change; P=0.011; VEGF: 2.84±2.19 vs. 0.79±0.62 fold change; P=0.030; HGF: 8.72±6.99 vs. 1.12±0.71 fold change; P=0.049). Animals treated with active ECM biomaterial demonstrated functional recovery beyond inactive ECM biomaterial treated animals (EF: 40.50±7.47% vs. 32.74±9.31%; P=0.022). Increased vascularity was observed within the infarcted myocardium of active ECM biomaterial treated animals (active: 16.56±2.97 vs. inactive: 10.81±2.23 blood vessels per high power field; P<0.001). In vitro, active ECM biomaterial also increased vascular network formation of human endothelial cells seeded in matrigel compared to inactive ECM biomaterial (total tubule length: 26.30±2.78mm vs. 21.98±2.86mm; P=0.009).

Conclusion: These data demonstrate that ECM biomaterial stimulates vasculogenesis through a FGF-2 dependent paracrine mechanism. This bio-inductive mechanism results in attenuated adverse LV remodeling and enhanced functional recovery when ECM biomaterial is applied following ischemic injury.
Figure 7

Infarcted Myocardium
Bioactive ECM Scaffold

FGF-2
Vasculogenic Growth Factors: FGF-2, VEGF, HGF

Cardiac Myofibroblast
New Blood Vessel
Cardiac Myocyte
Epicardial Progenitor Cell
ECM
DOXORUBICIN TREATMENT OF YOUNG MICE INDUCES HYPERTENSION AND LATE-OCCURRING CARDIAC DYSFUNCTION IN RESPONSE TO CARDIAC STRESS

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Background: Over the past 40 years, advancements in the diagnosis and treatment of cancer have increased survival rates in children diagnosed with cancer. Anthracyclines, such as doxorubicin (DOX) are among the most effective chemotherapies used in the treatment of pediatric cancers. However, the clinical utility of DOX is offset by its well-known cardiotoxicity, which often does not appear until later in life. Indeed, despite improved cancer survival rates, children treated with DOX have an increased likelihood of developing cardiomyopathy in adulthood. Unfortunately, little is known about the mechanism behind this delayed cardiotoxicity. Since a higher incidence of hypertension has been observed in adult cancer-survivors treated with DOX, we investigated whether juvenile DOX exposure impaired the ability of mice to adapt to angiotensin II (ANGII)-induced hypertension later in life.

Methods: 4-week old young mice were intraperitoneally administered a low dose of DOX (4 mg/kg) or saline once a week for 3 weeks and then left to recover for 5 weeks. Following the 5-week recovery period, mice were infused with a low or high dose of ANGII or vehicle for 2 weeks. Radiotelemetry, echocardiography and immunoblotting were used to measure blood pressure, cardiac structure/function and cardiac stress markers, respectively.

Results: Despite an exhaustive molecular analysis of hearts from DOX-treated mice, only p38 mitogen-activated protein kinase was activated at 1 week after the last DOX injection. Five weeks following the last DOX/saline administration, there was no change in cardiac structure or function between groups, suggesting that our low dose DOX regimen only caused damage at the molecular level. After low dose of ANGII infusion, both saline and DOX-treated mice displayed hypertension but only DOX-treated mice failed to develop compensatory hypertrophy in response to this increased hemodynamic load. Despite no DOX-induced overt cardiomyopathy at 5 weeks post-DOX administration, DOX-treated mice did not survive the severe hypertension induced by a high dose of ANGII, while all saline-injected mice survived.

Conclusion: We have developed a young mouse model of DOX-induced cardiotoxicity that demonstrates no overt physiological damage early in life but results in an impaired ability of the adult heart to adapt to pathological stress such as hypertension. This clinically relevant mouse model will allow us to characterize the molecular mechanism behind late-onset DOX-induced cardiotoxicity as well as investigate potential pharmacological interventions administered at the time of DOX treatment that may protect the heart from late onset cardiac dysfunction.
ANGIOSTATIN’S HYPOXIC-SPECIFIC EFFECTS ON PRO-MMP-2 AND ENOS IN HUMAN CARDIAC MICROVASCULAR ENDOTHELIAL CELLS

Natasha Govindasamy, Natasha Lifoso, Paul Jurasz

Background: Angiostatin is a platelet-generated anti-angiogenic mediator. In hypoxia, angiostatin inhibits endothelial cell (EC) matrix metalloproteinase (MMP)-2 expression and migration. Angiostatin may contribute to endothelial dysfunction as it inhibits endothelial nitric oxide synthase (eNOS) expression. As reduced eNOS expression and NO biosynthesis has been reported for endothelial cells of Type II diabetics (T2D), and NO protects endothelial cells from apoptosis, our objective was to compare angiostatin’s anti-angiogenic effects on ECs from non- and T2D. We hypothesized that in hypoxia angiostatin will decrease the expression of angiogenesis mediators eNOS and MMP-2 within ECs from non-diabetic individuals, but that due to already reduced NO-mediated survival signaling it will induce death of T2D ECs. In vivo, excess angiostatin will decrease blood flow recovery in a hind limb ischemia model.

Methods: Human cardiac microvascular ECs (HMVEC-C) were treated with angiostatin (600nM) or phosphate-buffered saline (PBS) and incubated under hypoxic conditions. MMP-2 and eNOS levels were determined by immunoblot. Transgenic eNOS-GFP mice were administered angiostatin (30μg) or PBS and underwent femoral artery ligation. Blood flow was measured by laser Doppler scanner. Gastrocnemius muscle tissue was collected from hind limbs of mice for confocal microscopy of eNOS-GFP and MMP-2. HMVEC-C from non-diabetic and T2D were treated with angiostatin (600nM) under hypoxic conditions and apoptosis and necrosis was measured via flow cytometry.

Results: Angiostatin caused attenuation of MMP-2 (35±9% reduction) and eNOS (53±14% reduction) expression in hypoxic non-diabetic HMVEC-C vs. PBS control. An injection of angiostatin in mice reduced blood flow recovery to the ischemic limb on day 14 (30±0.08% reduction). Confocal microscopy of ischemic gastrocnemius muscle tissue from angiostatin-treated mice exhibited decreased eNOS-GFP fluorescent intensity, along with reduced staining of MMP-2 when compared to control mice. During hypoxia angiostatin induced necrosis of T2D ECs (6.98±2.1% vs non-diabetic 3.03±0.3%).

Conclusion: Our data suggests that in hypoxia angiostatin inhibits expression of angiogenesis mediating proteins by non-diabetic ECs; whereas, it induces necrosis of T2D ECs. This may be due to loss of NO-mediated survival signaling in T2D ECs. Furthermore, excess angiostatin in an in vivo model of hind limb ischemia results in reduced recovery blood perfusion, which could be a result of decreased levels of angiogenic mediators, eNOS and MMP-2. From a therapeutic perspective, angiostatin may be an important target to neutralize to promote angiogenesis, particularly in T2D.
GENETIC DELETION OF SOLUBLE EPOXIDE HYDROLASE PRESERVES MITOCHONDRIAL EFFICIENCY AND CARDIAC FUNCTION POST-MI IN AGED MICE

Lockhart Jamieson, Victor Samokhvalov, Maria Akhonkh, Kyra Lee, Woo Jung Cho, Abhijit Takawale, Xiuhua Wang, Zamaneh Kassiri, John Seubert

**Background:** Pathophysiological responses, including cardiovascular complications, often alter with age. Cardioprotective effects of epoxyeicosatrienoic acids (EETs) toward acute myocardial ischemia-reperfusion injury have been well documented. However, biological relevance of EET-evoked cardioprotection in the ageing myocardium remains unknown. EETs are metabolized to less active metabolites by the enzyme soluble epoxide hydrolase (sEH). This study uses permanent occlusion of the left anterior descending coronary artery (LAD) in young and aged sEH null and WT mice to compare cardiac and mitochondrial function following ischemic injury.

**Methods:** Age-matched 16 month old (aged) and 3 month old (young) sEH null and littermate wild-type (WT) mice were subjected to permanent LAD occlusion. Echocardiography was used to assess cardiac structure and function prior-to and 7 days post-myocardial infarction with tetrazolium chloride staining to determine infarct size. Mitochondrial ultrastructure was obtained using electron microscopy. Caspase-3, 20S proteasome, aconitase and mitochondrial ETC enzymatic activities were ascertained using established protocols. Mitochondrial respiration was assessed using a Clark electrode in permeabilized cardiac fibers to obtain respiratory control ratios.

**Results:** Markers of cell injury, mitochondrial efficiency and overall cardiac function were preserved in aged sEH null mice, although less robustly than in their young counterparts. While aged animals of both genotypes demonstrated a similar overall age-related decline, sEH deletion conferred protection from myocardial ischemic injury regardless of age.

**Conclusion:** Our data demonstrate the protection originating from sEH deletion in aged mice was reduced compared to young animals, signifying unavoidable deleterious consequences of biological ageing on cardiac function.
THE CARDIAC TROPONIN I SWITCH REGION IN A MANNER THAT COULD ACCOUNT FOR MYOCARDIAL STUNNING

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Background: Myocardial stunning is a period of reversible contractile dysfunction that can occur in viable heart tissue following ischemia-reperfusion (I/R) injury. Intracellular matrix metalloprotease-2 (MMP-2) has been shown to proteolyze cardiac troponin I (cTnI) during I/R injury of isolated rat hearts. Inhibition of MMP-2 attenuated cTnI proteolysis and improved cardiac function post-reperfusion. Cardiac troponin is a trimeric complex consisting of cTnI, troponin C (cTnC) and troponin T (cTnT). During systole, calcium-bound cTnC binds to the switch region, cTnI_{146-158}*, releasing the inhibitory effect of cTnI and allowing actin-myosin cross-bridging and contraction to proceed. The objective of this study is to understand the precise cleavage sites and effects of MMP-2 on cTnI to determine if it could potentially account for myocardial stunning. We hypothesize that MMP-2 mediated proteolysis of cTnI switch region can explain the unresolved mechanism of myocardial stunning.

Methods: As a full length purified protein, cTnI_{1-209} is insoluble. Therefore, soluble human cTnI_{1-77} and cTnI_{135-209} were synthesized in E. coli. The fragments contain known binding sites for cTnC and actin, which were further characterized by using solution nuclear magnetic resonance (NMR) on a 500 MHz spectrometer. cTnI_{1-77} and cTnI_{135-209} were incubated separately with activated human MMP-2 at 1:125 to 1:10000 (MMP-2: cTnI) molar ratios for 2 hr at 37°C. The MMP-2 inhibitor ARP-100 was used to block MMP-2 activity. Liquid chromatography-mass spectrometry was used to map the MMP-2 cleavage sites in cTnI. MMP-2 proteolysis of cTnI was also assessed in the presence of cTnI binding partners, cTnC and actin.

Results: MMP-2 proteolysis of cTnI revealed multiple cleavage sites within cTnI, generating 1-17, 157-199, and 200-209 fragments. The N-terminal cleavage site 12RPAPAP↓IRRRSS_{23} lies within the cardiac-specific region of cTnI, just N-terminal to the cTnI_{19-37} region shown by NMR to interact with the regulatory N-domain cTnC. MMP-2 cleavage at the second cTnI site, 152AMMQAL↓LGARAK_{163}, would be expected to disrupt the calcium-dependent binding of the switch region, cTnI_{146-158}* to cTnC. MMP-2 cleavage here was partially inhibited by calcium-saturated cTnC binding to cTnI, and completely inhibited by actin binding, consistent with our NMR data showing that this region of cTnI can interact alternatively with cTnC or actin.

Conclusion: We demonstrated here the precise location of MMP-2 cleavage sites in human cTnI. Of particular interest, one cleavage site was located in the cTnI switch region. Since the switch region is needed for activation of cardiac muscle contraction, cleavage here could potentially account for myocardial stunning.
IHD-BAS-4

DIFFERENTIAL EFFECT OF 19,20-EPOXYDOCOSAPENTANOIC ACID (EDP) IN H9C2 CELLS GROWN IN HIGH OR LOW GLUCOSE CONDITIONS

Tomoko Endo, Victor Samokhvalov John M. Seubert

Background: The importance of dietary polyunsaturated fatty acids (PUFAs) in the reduction of cardiovascular disease has been recognized for many years. Epoxydocosapentanoic acids (EDPs) are lipid mediators produced by cytochrome P450 epoxygenase from docosahexaenoic acids (DHA). In this study, we investigated the impact of normal and low glucose concentrations toward 19,20-EDP-mediated effects in normoxic conditions in H9c2 cells.

Methods: H9c2 cells were cultured in DMEM containing either normal (25mM) or low (5.5mM) glucose concentrations and supplemented with 10% fetal bovine serum (FBS), 1% penicillin and streptomycin at 37°C (5% CO2/65% N2). Cells were treated with 0 or 1µM 19,20-EDP, 100µM DHA, 1µM Myriocin and subjected to 24h normoxic. Cellular viability was assessed by the reduction of a luciferase substrate by metabolically active cells. Cell lysates were assessed for caspase-1/3 activity using a profluorogenic peptide Ac-WEHD-AMC and Ac-DEVD-AMC. Extracellular oxygen consumption rates (OCR) were assessed using a phosphorescent oxygen sensitive reagent. Mitochondrial respiration was measured using Clark oxygen electrode connected to Oxygraph Plus recorder. Autophagy was detected using monodansylcadaverine (MDC), the fluorescent marker for lysosomal/ autophagic vacuoles. Different fractionation methods were performed to measured the ceramide level by LC/MS.

Results: H9c2 cells cultured under normal (25mM) glucose conditions and treated with 19,20-EDP demonstrated significant loss in cell membrane integrity, decreased MTT reduction, increased proteasomal, caspase activity, autophagy, ceramide level as well as decreased OCR and ATP. In contrast, H9c2 cells cultured in low glucose (5.5mM) conditions and treated with 19,20-EDP demonstrated increased MTT reduction and ATP production.

Conclusion: Our data suggest that cells cultured in high glucose conditions, a more ‘aerobic glycolytic’ state, are susceptible to 19,20-EDP induced cell death with autophagy. While in low glucose conditions, reflecting more oxidative phosphorylation, 19,20-EDP protected H9c2 cells.
Background: Myocardial ischemia is a major health issue where the heart receives insufficient oxygen to contract effectively, and subsequent reperfusion can lead to injury as the heart adapts to changes in oxygen availability. In ischemia, the heart increases rates of anaerobic glycolysis, which becomes uncoupled from glucose oxidation, and glucose and fatty acid oxidation rates are reduced. In reperfusion, fatty acid oxidation rates increase dramatically to become the major source of energy production, while glucose oxidation rates remain low. This leads to a metabolically inefficient heart, as glucose oxidation requires less oxygen to produce ATP than fat. The activity of metabolic enzymes can be affected by post-translational modifications. Specifically, lysine acetylation of fatty acid oxidation enzymes has been shown to increase their activity. The acetylation of metabolic enzymes has been associated with heart failure and disease, while acetylation status in the process of ischemia and reperfusion is unknown. In this study, we used an isolated working heart rat model to measure differences in cardiac energy substrate metabolism occurring during ischemia and reperfusion. We also compared protein lysine acetylation of animals undergoing aerobic perfusion and others undergoing ischemia and reperfusion. We administered the compound Honokiol, a suggested activator of the deacetylase enzyme SIRT3, to see if acutely altering acetylation status during ischemia and reperfusion could affect substrate metabolism and efficiency.

Methods: Sprague Dawley rats were anaesthetized, and their hearts were excised and cannulated in an isolated working heart perfusion model. Ischemia-Reperfusion hearts were perfused using radiolabeled palmitate and glucose for 30 minutes, followed by 30 minutes of induced no-flow ischemia, and 40 minutes of reperfusion. Aerobic hearts were perfused for 100 minutes with the same radiolabeled substrates. Honokiol in DMSO (50uM) or Vehicle (DMSO) were added to the perfusate solution. Metabolic rates of fatty acid oxidation, glucose oxidation and glycolysis were measured, as well as cardiac function. Biochemical analysis was performed by immunoprecipitation and western blot to measure acetylated and total protein expression.

Results: Control animals that underwent ischemia and reperfusion had significantly higher amounts of overall acetylation compared to aerobically perfused controls (p<0.05). Fatty acid oxidation and glucose oxidation rates were not different between control or honokiol-treated groups following ischemia (392 ± 212 vs. 430 ± 96 nmol ³H palmitate*g dry wt⁻¹*min⁻¹, control vs. honokiol, respectively and 189 ± 34 vs. 303 ± 91 nmol ¹⁴C glucose* g dry wt⁻¹*min⁻¹ control vs. honokiol, respectively), suggesting that Honokiol did not appear to have an acute significant effect on acetylation in the perfusion time frame.

Conclusion: While metabolic rates did not differ significantly between control and honokiol-treated groups, there was a significant increase in overall acetylation that occurred following ischemia and reperfusion when compared to aerobic controls. This provides evidence that acetylation increases in the heart following ischemia and reperfusion. Increases in acetylation of proteins following ischemia and reperfusion may potentially have some causatory effect on increased fatty acid oxidation rates and subsequent reduction in cardiac efficiency that occurs following ischemia and reperfusion in patients.
Background: Cardiovascular disease (CVD) represents the number 1 cause of death in type 2 diabetes (T2D) patients. This includes diabetic cardiomyopathy, of which there are no approved therapies. Previous studies have shown that myocardial glucose oxidation rates are markedly impaired during T2D due to reduced pyruvate dehydrogenase (PDH) activity. Furthermore, forkhead Box O1 (FoxO1) activity is enhanced in T2D and has been shown to increase expression of PDH kinase 4 (gene name Pdk4), which phosphorylates and inhibits PDH activity. Because the role of FoxO1 on glucose oxidation impairment during diabetic cardiomyopathy has not yet been assessed, our aim is to determine whether FoxO1 controls Pdk4 transcription, and whether its inhibition preserves PDH activity and glucose oxidation in the heart.

Methods: FoxO1 activity was modulated in differentiated H9c2 cardiac myocytes, following which Pdk1/2/4/PDHK4 expression and PDH phosphorylation/activity were assessed. We also assessed binding of FoxO1 to the Pdk4 promoter in cardiac myocytes via electrophoretic mobility shift, luciferase, and chromatin immunoprecipitation assays, while examining the role of FoxO1 on glucose oxidation in the isolated working heart.

Results: Both pharmacological (1 µM AS1842856) and genetic (siRNA-mediated) inhibition of FoxO1 decreased Pdk4/PDHK4 expression and subsequent PDH phosphorylation/activity were assessed. We also assessed binding of FoxO1 to the Pdk4 promoter in cardiac myocytes via electrophoretic mobility shift, luciferase, and chromatin immunoprecipitation assays, while examining the role of FoxO1 on glucose oxidation in the isolated working heart.

Conclusion: Our results suggest that FoxO1 is a direct regulator of Pdk4 transcription in the heart, thereby controlling PDH activity. Thus, FoxO1 antagonism may represent a novel approach to mitigate diabetic cardiomyopathy via augmenting myocardial glucose oxidation rates.
Background: The Low-density lipoprotein receptor (LDLR) plays a very critical role in the clearance of plasma LDL cholesterol (LDL-C) and as such regulates cholesterol homeostasis in the body. Mutations in LDLR cause familial hypercholesterolemia (FH), which is characterized by elevated circulating levels of cholesterol, specifically LDL-C. Hypercholesterolemia has been strongly correlated to the risk of cardiovascular disease. The ectodomain of LDLR can be cleaved by proteases, with the released soluble ectodomain detected in cell culture media and in human plasma. Serum levels of this soluble ectodomain are positively correlated with plasma LDL-C levels. However, the protease(s) responsible for LDLR cleavage has not been identified.

Methods: Cells were transfected with siRNA targeting MT1-MMP, Wild type and E240A MT1-MMP cDNA. Co-immunoprecipitation experiment was done to determine association between LDLR and MT1-MMP. In vivo, adeno associated virus delivered shRNA was used to effect MT1-MMP knockdown, in mice. Similarly, overexpression of MT1-MMP in mice was done through adeno virus delivery.

Results & Conclusion: Inhibiting the expression of the extracellular matrix degrader, Membrane type-1 Matrix Metalloproteinase (MT1-MMP) increases LDLR abundance, while overexpression of wild type MT1-MMP, but not the enzymatically dead mutant E240A, reduces it in cultured cells and mice. We also found that MT1-MMP directly associates with LDLR and promotes the LDLR ectodomain cleavage. Taken together, these findings demonstrate that MT1-MMP proteolytically cleaves LDLR.
VASD-BAS-1

PORPHYROMONAS GINGIVALIS-INCREASED ATHEROSCLEROSIS IS TRANSFERRED BY BONE MARROW TRANSPLANT

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Background: Periodontal disease (PD) is a destructive inflammatory disease of the periodontium and Porphyromonas gingivalis (Pg) is a keystone pathogen in its early onset. Mounting evidence supports a role for PD as an independent risk factor for atherosclerosis. In human studies, after successful PD treatment, cardiovascular disease event risk is not decreased, suggesting that PD risk persists after pathogen elimination. This may be due to long term changes in immune cells and their precursors. In PD and atherosclerosis, macrophages are the important disease-causing immune cells. Our previous work showed that PD in an atherosclerosis mouse model significantly increased lesion burden.

Methods: Using the Low Density Lipoprotein Receptor Knock-out (LDLR⁻) mouse model of atherosclerosis, we transplanted BM from mice with western diet-induced atherosclerosis that were either infected with Pg or sham treated, to naïve LDLR⁻ mice. At study midpoint, we collected blood for cholesterol and cytokine analyses. After 16 weeks, we collected blood and dissected, stained and scanned the aortas for en face morphometric analysis using Adobe Photoshop, software. The relative expression levels of 40 mouse cytokines in blood plasma that was collected at sacrifice, were determined using The Mouse Cytokine Array Panel A.

Results: Our results showed that mice receiving BM from donors experimentally infected with Pg had significantly greater atherosclerotic lesion burden compared with mice receiving BM from sham infected mice. In male mice, pro-inflammatory cytokines; G-CSF, C5/C5a and TREM-1 were 1-5 fold higher in mice receiving BM from donors experimentally infected with Pg. Importantly, there were no differences in weight, blood glucose or cholesterol levels between the groups.

Conclusion: Our results suggest that increased atherosclerosis as a result of PD can be transferred by BM cells, and that the systemic long term PD effect may in part be due to changes induced in the BM. These changes might be epigenetic modifications in inflammatory genes and macrophage precursor cells which we are currently studying.
THE FUNCTIONAL CONTRIBUTION OF MYOENDOTHELIAL FEEDBACK TO ARTERIAL TONE IS DETERMINED BY THE NATURE OF THE VASOCONSTRICTION

Paul Kerr, Ran Wei, Stephanie E Lunn, Stephen L Gust, Boyd Classen, Timothy V Murphy, Shaun L Sandow, Frances Plane

Background: Constriction of resistance arteries in response to global application of agonists is modulated by activation of the endothelium via myoendothelial feedback. Recent evidence supports a model of myoendothelial feedback in which generation of localized InsP$_3$-dependent Ca$^{2+}$ transients leads to activation of intermediate conductance Ca$^{2+}$-activated K$^+$ (IKCa) channels to hyperpolarize the endothelium. We have now investigated the functional contribution of this pathway to limiting responses to two physiologically important stimuli, activation of sympathetic nerves and increases in intravascular pressure.

Methods: Wire myography: Endothelium-intact segments of third order mesenteric artery were mounted in a Mulvany-Halpern myograph for recording of changes in isometric tension. Platinum electrodes were placed either side of the vessel to allow transmural stimulation of perivascular nerves at 0.25 to 20 Hz at 5 min intervals. Pressure myography: Leak-free segments of 3rd order mesenteric artery were mounted between two glass cannulae in an arteriograph chamber under conditions of no luminal flow. Following a 30 min equilibration period, pressure ramps were applied by increasing the pressure to 120 mmHg in increments of 20 mmHg. At the end of each experiment arteries were bathed in Ca$^{2+}$ free Krebs buffer to reveal the maximum passive diameter. Nerve-evoked vasoconstriction in the rat perfused mesenteric bed: The mesenteric vascular bed was perfused with oxygenated Krebs buffer at 5 ml/min. Changes in perfusion pressure were measured with a pressure transducer and perivascular nerve stimulation at 1 to 40 Hz was applied at 10 min intervals. Data analysis: All values are shown as mean ± SEM for n rats. Statistical differences between mean values were determined using Student’s t-test or ANOVA.

Results: In isolated segments of rat mesenteric resistance artery, pharmacological inhibition of IKCa channels significantly potentiated increases in tone elicited by global application of noradrenaline, but did not significantly alter increases in tone elicited by stimulation of sympathetic perivascular nerves, or myogenic reactivity elicited by stepwise increases in intravascular pressure. Similarly, in the endothelium-intact perfused mesenteric bed, blockers of IKCa channels enhanced vasoconstriction to exogenous noradrenaline but had no effect on nerve-evoked vasoconstriction. However, the influence of the endothelium on responses to sympathetic nerve stimulation was inhibited by blockers of nitric oxide signaling and by inhibition of small conductance Ca$^{2+}$-activated K$^+$ (SKCa) channels.

Conclusion: The functional role of IKCa channel-mediated myoendothelial feedback may be limited to controlling diameter of individual arterial segments to enable blood flow to be locally tuned to discrete regions. In contrast, shear stress-induced activation of SKCa channels may responsible for the global endothelial response to stimulation of sympathetic nerves that governs the magnitude and distribution of tissue blood flow at the level of the intact vascular bed.
Background: Atherosclerosis, or hardening of the arteries, is a chronic inflammatory process, which leads to heart disease and death. Asymptomatic apical periodontitis (AP) is a common inflammatory condition, associated with infected teeth. In a recent systematic review, we identified a compelling number of studies that link AP with a higher prevalence of cardiovascular diseases in humans; however, no studies examined causality. Performing these studies in humans is challenging, therefore we use a mouse model to investigate the causal relationship between AP and atherosclerosis. To our knowledge, this is the first study that uses an atherosclerotic mouse model to examine the influence of AP. Our hypothesis is that systemic inflammation and atherosclerosis will be higher in mice with AP compared to mice without AP.

Methods: Low density lipoprotein receptor knockout (LDLR KO) mice are a classic atherosclerosis model, which develop lesions similar to humans when fed a high fat diet. To study the influence of AP on systemic inflammation and atherosclerosis, AP is induced by exposing the dental pulp of the 4 first molars in each mouse, (group 1, n=14); controls receive only anesthesia and no teeth are drilled (group 2, n=14). All mice are fed a high-fat diet to induce atherosclerosis. After 16 weeks, the mice are euthanized and blood, aorta as well as maxilla and mandible are collected. AP lesions are validated and characterized by Micro-computed tomography (micro-CT) scans and histology. Our outcome measures are atherosclerosis in the aorta (expressed as the percentage of area stained with oil red O for lipid), plasma systemic inflammation (by a panel of 40 cytokines array) and oxidative stress (by the levels of 3-nitrotyrosine using ELISA). Baseline control (no AP induction, group 3, n=5) and midterm measurements (8 weeks after AP induction, group 4, n=5) are also evaluated.

Results: The micro-CT scans of the maxilla and the mandible, taken 8 weeks after dental pulp exposure, confirm successful establishment of AP lesions in the LDLR-KO mice (n=3). Normal teeth and normal apical tissues were present in the baseline group. In addition, mice in the AP group (n=5) as well in the control group (n=4) have successfully reached the end point of the study (16 weeks) and are currently being processed for analysis.

Conclusion: Our results demonstrate the feasibility of AP induction in LDLR-KO mice. Additionally, it was demonstrated that the mice can successfully reach the long term end point of the study (16 weeks) without substantive issues. More samples are being collected and the results will be analyzed as we proceed. Overall, this study has the potential to provide the first evidence for a causative relationship between AP and atherosclerosis. Since AP often goes unnoticed by patients and physicians, they would benefit from increased awareness about the potential impact of oral infections on systemic health and apply screening modalities and dental treatment for AP in patients with increased risk for cardiovascular diseases.
VALIENTA BACK, GABRIELA LESYK, FRANCES PLANE, PAUL JURASZ

**PHARMACOLOGICAL CHARACTERIZATION OF THE FUNCTIONAL ROLE OF CALCIUM-ACTIVATED POTASSIUM CHANNELS IN PLATELETS**

**Background:** In arteries, stimulation of endothelial cell small (SK$_{Ca}$) and intermediate (IK$_{Ca}$) conductance calcium-activated potassium channels provides a negative-feedback mechanism to limit agonist-induced vasoconstriction. Additionally, endothelial cell K$_{Ca}$ channels in conjunction with nitric oxide (NO) mediate vasodilation in response to agonists and physical stimuli. Platelets, like endothelial cells, possess K$_{Ca}$ channels and generate NO via endothelial nitric oxide synthase (eNOS). NO is known to limit platelet aggregation but the role of KCa channels in platelet function and NO-generation has not been explored. Our hypothesis was that activation of K$_{Ca}$ channels would inhibit platelet aggregation and enhance platelet NO production. Our objective was to pharmacologically characterize SK$_{Ca}$ and IK$_{Ca}$ channel function in platelets, and investigate their role in platelet NO production.

**Methods:** Platelets were isolated from the blood of healthy volunteers and aggregometry performed in the presence of SK$_{Ca}$ (CyPPA) and IK$_{Ca}$ (SKA-31) channel activators. Dense granule secretion was measured by ATP chemiluminesence. DAF-FM flow cytometry was used to measure NO generation.

**Results:** CyPPA and SKA-31 inhibited collagen-induced aggregation in a concentration dependent manner. IK$_{Ca}$ selective channel blocker reversed the anti-aggregatory effects of 10µM SKA-31 but not CyPPA. SK$_{Ca}$ channel-selective blocker did not reverse the effect of either CyPPA or SKA-31. CyPPA and SKA-31 inhibited NO generation back to basal resting platelet levels. CyPPA and SKA-31 demonstrated similar inhibitory effects on platelet dense granule secretion, whereas only SKA-31 significantly inhibited alpha granule secretion.

**Conclusion:** Activation of SK$_{Ca}$ and IK$_{Ca}$ channels inhibits both platelet aggregation and platelet NO generation. Furthermore, the use of selective blockers suggest that IK$_{Ca}$ is the dominant K$_{Ca}$ channel within platelets. These data indicate that K$_{Ca}$ channels may provide novel targets for therapeutics to inhibit platelet aggregation.
**TARGETING PYRUVATE DEHYDROGENASE KINASE WITH DICHLOROACETATE IN PULMONARY ARTERIAL HYPERTENSION: A VARIABLE CLINICAL RESPONSE DRIVEN BY GENETIC POLYMORPHISMS IN SIRTUIN 3 AND UNCOUPLING PROTEIN-2**

Vikram Gurtu, Linda Webster, Adam Kinnaird, Aristeidis Boukouris, Kyoko Hashimoto, Trevor Stenson, Alois Haromy, Christopher White, Jayan Nagendran, Darren Freed, Martin Wilkins, Evangelos Michelakis

**Background:** Suppressed mitochondrial function inhibits apoptosis, promotes proliferation in the vascular remodeling of pulmonary arterial hypertension (PAH) and is largely due to inhibition of pyruvate dehydrogenase (PDH) by PDH kinase (PDK) induction. Additional causes of PDH inhibition include inhibition of Sirtuin3 (Sirt3; acetylates and activates PDH), and Uncoupling Protein 2 (UCP2; increases mitochondrial calcium). Sirt3 and Ucp2 KO animals develop spontaneous PAH and common loss-of-function polymorphisms in both genes are associated with clinical metabolic syndrome. In a phase-2 trial of 16 PAH patients, the PDK inhibitor Dichloroacetate (DCA) showed variable efficacy in decreasing mean PA pressure (mPAP), not due to DCA-level differences in responders/non-responders. We hypothesize that PDK is upregulated in human PAH but Sirt3/Ucp2 polymorphisms cause resistance to DCA.

**Methods:** PDK expression, PDH activity and mitochondrial respiration were studied in 10 archived human lungs (6 PAH, 4 controls) and 5 human lungs from lung transplant recipients acutely studied with ex-vivo lung perfusion (EVLP). The presence of Ucp2 (rs659366) and Sirt3 (rs11246020) polymorphisms were studied using PCR. A score of 0 was given if both alleles were wild-type; a score of 4 if both alleles had the polymorphisms in both genes; intermediate genotypes received 1-3 scores.

**Results:** PDK was upregulated in lung tissue and media of pulmonary arteries, and PDH activity was inhibited in PAH lungs compared to controls. In EVLP, DCA increased PDH activity and mitochondrial respiration in lungs with low polymorphism score (0-1), but not in a lung with a high score of 3. In patients enrolled in the clinical trial, lower scores correlated with higher reductions in mPAP (Figure, Spearman correlation rS= 0.654, p=0.006).

**Conclusion:** PDK is induced in human PAH contributing to PDH inhibition but the ex-vivo and clinical response to DCA is limited by polymorphisms that inhibit PDH in a non-PDK dependent manner. This is the first example of precision medicine in PAH, where the clinical response to a drug is driven by the patient genotype.
Figure: Polymorphisms in UCP2 and SIRT3 Can Result in PDK Independent Inhibition of PDH, Limiting the Response to DCA

Responder
DCA
Non-Responder
\(\downarrow\text{UCP2}
\text{SNP rs659366}
\)
PDK
\(\downarrow \text{SIRT3}
\text{SNP rs11246020}
\)
PDH
Glucose Oxidation

\[\begin{align*}
\Delta \text{mPAP (mmHg)} &= \text{Spearman Coefficient:} \\
\ &\ r_s = 0.654 \\
\ &\ p = 0.006
\end{align*}\]

LEGEND:
- UCP2 Heterozygous
- UCP2 Homozygous
- SIRT3 Heterozygous
- SIRT3 Homozygous
VASCULAR DAMAGE IN EX VIVO KIDNEY PERFUSION

Yilun Wu, Darren H. Freed

Background: Organ transplantation is the definitive therapy for chronic, end-stage organ failures such as end-stage kidney failure. Marginal donor kidneys, such as kidneys from donation after circulatory determination of death, often suffer from insufficient in situ perfusion and ischemia. Ischemia and reperfusion in transplant procedures can also lead to tissue and vascular damage, the resulting kidney graft is more likely to suffer from primary dysfunction. The ever-increasing shortage in donor kidney supply necessitates innovative techniques to rescue marginal donor organs for transplantation. Normothermic Ex Vivo Kidney Perfusion (NEVKP) is a novel organ preservation technique, where the kidney is machine perfused at normothermia instead of hypothermia in the traditional techniques. NEVKP provides an opportunity to both assess and treat vascular damage in an isolated, ex vivo environment. Though NEVKP’s clinical implementation is in its infancy, it has been shown to provide superior preservation compared to the traditional cold preservation techniques.

Methods: We have established a large animal model of NEVKP to investigate the effects of different perfusion methods (normothemic versus hypothermic) and the addition of dextran-40 on vascular and kidney damage. Dextran-40 is a glucan with anticoagulant properties and has protective effects on the endothelium.

Results & Conclusion: To date, we have successfully perfused 8 kidneys in the NEVKP system. Perfusate and urinary concentrations of von Willebrand Factor is used to measure vascular endothelial damage. Perfusate and urinary concentrations of kidney injury molecular-1 (KIM-1) is used to measure kidney damage. If normothermic ex vivo kidney perfusion can be used to evaluate and reduce vascular and tissue damage in kidney preservation for transplantation, it may translate to increased graft function and the ability to treat dysfunctional organs ex vivo.
CHARACTERIZATION OF MEGAKARYOCYTE SUBPOPULATIONS BASED ON THE HETEROGENEITY OF ENOS SIGNALLING; EFFECTS OF CYTOKINES ON MEGAKARYOCYTE ENOS AND INOS EXPRESSION

Gabriela Lesyk, Teresa Fong, Paul Jurasz

**Background:** Recently, our laboratory has identified in human blood two platelet subpopulations based on the presence or absence of a functional endothelial nitric oxide synthase (eNOS)-signalling pathway. We have also found that eNOS-negative platelets, although less abundant are more reactive than eNOS-positive platelets and initiate aggregate/thrombus formation. Since platelets derive from bone marrow megakaryocytes, we have decided to test the hypothesis that eNOS-negative and eNOS-positive subpopulations of megakaryocytes exist and give rise to their respective eNOS-based platelet subpopulations. Additionally, we have also tested whether pro- and anti-inflammatory cytokines have an effect on eNOS and inducible NOS (iNOS) levels within megakaryocytes as cytokines are known to regulate expression of eNOS and iNOS

**Methods:** The megakaryoblastic cell line (Meg-01) was used for experiments in place of megakaryocytes. To validate presence of eNOS within Meg-01 cells RT-PCR was performed, and gel samples were excised and sent for DNA sequencing. Flow cytometry was used to measure eNOS levels via intracellular immunofluorescence and nitric oxide production using cell-permable fluorescent probe DAF-FM (10μM) in Meg-01 cells. Additionally, Meg-01 cells were treated for 48 hours with IFNγ (10ng/ml) alone and with increasing concentrations of IL-10 (0.1-100ng/ml) and iNOS and eNOS levels were measured by Western Blot and RT-qPCR.

**Results:** Following RT-PCR and agarose gel electrophoresis a detected cDNA 241 bp band was confirmed to be eNOS via DNA sequencing. Flow cytometry results showed that similarly to platelets Meg-01 cells consist of two eNOS-based subpopulations, eNOS-positive (91.5%±1.2)/nitric oxide-producing (DAF+ve 92.0%±3.34) and eNOS-negative (8.5%±1.2)/nitric oxide-nonproducing (DAF-ve 8.0%±6.68) Meg-01 cells. In experiments with cytokines IFNγ (10ng/ml) increased level of iNOS within Meg-01 cells and higher concentrations of IL-10 (10-100ng/ml) nullified that effect. eNOS levels were not detectable using Western Blot, however qPCR results showed 6.4 fold decrease of eNOS levels following IFNγ and only 2.2 fold decrease with IL-10 (100ng/ml).

**Conclusion:** Megakaryocyte subpopulations exist within Meg-01 cell line based on the presence or absence of functional eNOS. Pro-inflammatory cytokine IFNγ enhanced iNOS expression and decreased eNOS expression in Meg-01 cells; however, high concentrations of IL-10 attenuated the effect. These preliminary data show that action of pro-inflammatory IFN-γ may promote growth/differentiation of megakaryocytes with decreased levels of eNOS, which may lead to formation of higher numbers of more reactive eNOS-ve platelets leading to higher risk of prothrombotic state. Further experiments are required to confirm whether eNOS+ve and eNOS-ve megakaryocytes give rise to their respective platelet subtypes.
CLINICAL SCIENCE POSTERS
Background: Pulmonary atresia (PAtr) is a rare congenital cardiac defect associated with tetralogy of Fallot, and other more complex intracardiac pathologies. All affected infants require surgical intervention at birth in the form of a repair (e.g. tetralogy of Fallot type repair with conduit) or systemic-pulmonary shunt. When the source of pulmonary blood flow in PAtr is the patent ductus arteriosus (PDA), there is an important risk of proximal branch pulmonary artery (PA) stenosis related to ductal tissue that constricts at its origin, typically involving the PA ipsilateral to the PDA. Branch PA stenosis complicates the surgical and long-term outcome of affected infants with frequent poor growth of the vessel and need for multiple reinterventions to rehabilitate the vessel. The incidence and preoperative risk factors for PDA-related PA stenosis are not well-defined. Knowing prior to initial intervention if a patient has the potential for evolving PDA related PA stenosis is important in planning appropriate operative management and postoperative surveillance. We sought to identify preoperative features that predict important branch PA stenosis using echocardiography.

Methods: All patients with PAtr who had a PDA-dependent pulmonary circulation at birth and who underwent intervention in the Stollery Cardiac Program between January 2009 and June 2015 were identified through the Xcelera echo database. Preoperative echocardiograms were reviewed to identify features that predicted the development of PDA-related proximal PA stenosis. Postoperative echocardiograms and clinical charts were reviewed. Comparisons were made between patients who required intervention for ipsilateral branch PA stenosis within the first two years after initial surgical intervention and those who did not, to determine potential factors associated with risk of branch pulmonary artery stenosis.

Results: Seventy-six patients met inclusion criteria with a diagnosis of PAtr including 52 patients who underwent a systemic to pulmonary shunt as an initial procedure and 24 who underwent biventricular repair. Of those with initial systemic-pulmonary shunt, 15 underwent eventual biventricular repair, 7 underwent further single ventricle palliation and 2 a 1.5 ventricle repair. Forty-three (57%) developed branch pulmonary stenosis requiring reintervention and in 36 of these (84%) branch PA stenosis was related to PDA constriction and the other 16% were related to surgical complications. Twenty-four of 36 (67%) pts with duct related stenosis were found to have the branch pulmonary artery origins on different planes with an unusual course of the branch pulmonary artery receiving the ductal insertion. Further analysis and comparisons between groups is ongoing.

Conclusion: More than half of patients with a diagnosis of PAtr develop branch PA stenosis. 84% of all stenosis are related to ductal tissue insertion and 67% of this subset, have unusual planes of origin and courses of the branch PAs by echo. Further analysis is required to elucidate other echocardiographic features that may identify those at risk for branch PA stenosis.
CARDIAC REHABILITATION IN THE PEDIATRIC FONTAN POPULATION: DEVELOPING AN INTERVAL TRAINING PROGRAM USING A NOVEL TELEMEDICINE VIDEO GAME-LINKED EXERCISE PLATFORM

Michael Khoury, Peter Wood, Jennifer Conway, Gwen Rempel, Devin Phillips, Pierre Boulanger, Michael Stickland M, Andrew Mackie A, Nee Khoo

Background: With increasing survival of children with Fontan physiology, management has shifted its focus towards optimizing patient physical functioning and improving quality of life. Children with Fontan physiology are less physically active and have lower exercise tolerance than healthy children. Conventional aerobic exercise programs have not yielded improvements in exercise capacity and compliance to home programs have been suboptimal. Therefore, we sought to develop a novel high-intensity-interval training (HIIT) regimen for children with Fontan physiology, utilizing a supervised telemedicine video-game-linked platform to improve enjoyment and compliance.

Methods: We developed a custom pediatric telemedicine bike ergometer (MedBike) linked to a video game platform that provides a medical supervisor with a live-feed of patient video/audio, electrocardiograph, blood oximetry signals while allowing live modulation of patient work. There are two phases to the study. (1) To calibrate the MedBike, healthy adult subjects underwent a standard cardiopulmonary exercise test (CPET) and a MedBike assessment. (2) We recruited pediatric participants with Fontan physiology, age 10-18yo to assess tolerance of a 20min HIIT regimen based on an initial CPET assessment, safety of the HIIT program, reliability of remote supervision, and enjoyment of the Medbike. The training regimen was modulated throughout the session based on the relative perceived exertion on the part of the participant.

Results: Calibration of Medbike was achieved with 10 healthy adults subjects where no difference in VO2 at a given power outputs was found between Medbike and CPET confirming equivalence (Figure). Five children with Fontan physiology have been recruited thus far and 4 have completed MedBike assessments (Table 1). Mean baseline peak VO2 was 33.8 ml/kg/min (74.8% predicted), range 28ml/kg/min – 38.7ml/kg/min. All MedBike assessments were well tolerated with no arrhythmias or desaturations > 5%. Participants were able to tolerate exercise intervals at 70-100% of peak power output for 1-minute at a time for 7 intervals total. High satisfaction levels (5/5) and appropriate difficulty with the MedBike interval training session (Table 2). At no time was there a loss of technical feed of live signals during training session.

Conclusion: The MedBike is novel telemedicine exercise ergometer that has comparable accuracy to a medical CPET. The technology was robust and the interval training regimen in children with Fontan was safe and well-tolerated, while the video-game platform was entertaining to the participants. The Medbike is likely to improve compliance and is well suited to a supervised remote home exercise HIIT program to improve exercise capacity in children with Fontan physiology.
Figure. MedBike calibration compared with standard cardiopulmonary exercise test (CPET) ergometer. VO2 = oxygen consumption.

Table 1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Lesion</th>
<th>Fenestration</th>
<th>Saturation room air (%)</th>
<th>Vasoadaptive medication</th>
<th>Function</th>
<th>Residual lesions</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>F</td>
<td>Tricuspid atresia, normally related great vessels, VSD</td>
<td>Yes</td>
<td>94%</td>
<td>No</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>F</td>
<td>Double outlet right ventricle, mitral atresia, VSD, discordant atroventricular connections</td>
<td>Yes</td>
<td>88%</td>
<td>No</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>F</td>
<td>Unbalanced AVSD (dominant right ventricle), coarctation of the aorta</td>
<td>No</td>
<td>96%</td>
<td>Enalapril</td>
<td>Normal LV</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>F</td>
<td>Transposition of the great arteries, large VSD, straddling mitral valve</td>
<td>Yes</td>
<td>90%</td>
<td>No</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>M</td>
<td>Tricuspid atresia, malposed great arteries, VSD, hypoplastic aortic arch</td>
<td>No</td>
<td>96%</td>
<td>No</td>
<td>Normal</td>
<td>None</td>
</tr>
</tbody>
</table>

VSD: ventricular septal defect; AVSD: atrioventricular septal defect; LV: left ventricle; RV: right ventricle; Fenestration: a hole placed at the time of surgery providing a connection between the Fontan conduit and the atrium, allowing right to left shunting to maintain cardiac output at the expense of lower oxygen saturations.

Table 2. Questionnaire results

| Participant | Compared with CPET, MedBike (1: far less fun; 5: far more fun) | Set-up and user interface (1: complicated; 5: easy to use) | Exercise difficulty (1: too difficult; 3: just right; 5: too easy) | Communication with remote supervisor (1: too difficult; 5: very easy) | Video game (1: too boring; 5: very fun) | Compared with CPET, MedBike (1: less likely to exercise; 5: more likely to exercise) |
|-------------|---------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------------
| 1           | 5                                                             | 5                                                          | 2                                                             | 5                                                             | 4                                                             | 4                                                                                   |
| 2           | 5                                                             | 3                                                          | 4                                                             | 5                                                             | 4                                                             | 3                                                                                   |
| 3           | 5                                                             | 4                                                          | 3                                                             | 3                                                             | 5                                                             | 4                                                                                   |
| 4           | 5                                                             | 3                                                          | 3                                                             | 5                                                             | 5                                                             | 4                                                                                   |
| Mean        | 5                                                             | 3.8                                                       | 3                                                             | 4.5                                                           | 4.5                                                           | 3.75                                                                |
CHD-CLIN-3
CARDIOVASCULAR HEALTH OF OFFSPRING OF DIABETIC MOTHERS FROM THE FETUS THROUGH LATE INFANCY STAGES

Victor Do, Halima Alhashmi, Tina Ojala, Tim Colen, Silvia Goncalvez-Alvarez, Sandra Davidge, Najlaa Al Rajaa, Jesus Serrano-Lomelin, Lisa K Hornberger

Background: Infants of diabetic mothers (IDMs) develop left ventricular (LV) hypertrophy and mild diastolic dysfunction prenatally, and are at increased risk of adult cardiovascular disease (CVD). Whether fetal changes truly resolve has not been explored. The aims of our study were to determine if IDMs have myocardial hypertrophy and diastolic dysfunction in late infancy, have increased aortic stiffness, and if cardiovascular pathology of IDMs is associated with worse maternal glycemic control.

Methods: We longitudinally investigated myocardial and vascular health by echocardiography in offspring of pregestational DM pregnancies both prenatally (3 each, 20-40 weeks) and in infancy (2-6 weeks & 6-12 months). We compared LV posterior (LVPW) and septal (IVS) wall thickness, systolic and diastolic function and aortic stiffness (pulse wave velocity, PWV) between IDMs and pre and postnatal age-matched controls from healthy pregnancies, and collected maternal A1c values.

Results: 36 IDMs and 36 controls were prospectively recruited. Increased LVPW and IVS was present in DM fetuses from the midtrimester that persisted through both early and late infancy (p<0.01). Although increased LV Tei index was present in late gestation IDM, by late infancy LV function was comparable to controls. PWV was increased in late infancy in IDMs (3.7+/-1.2 vs 2.2+/-0.5m/s, p <0.001) which correlated with LVPW and IVS (R2 0.82 & 0.87, respectively, p <0.01). Late infancy PWV also correlated with 3rd trimester A1c (R2 = 0.83, p<0.01).

Conclusion: IDMs display persistence of LV hypertrophy through late infancy. Aortic stiffness is increased in IDMs in late infancy which relates to late gestation maternal glycemic control.
PRENATAL DIAGNOSIS IMPROVES THE PERIOPERATIVE CONDITION OF NEONATES REQUIRING SURGICAL INTERVENTION FOR COARCTATION BUT IS ASSOCIATED WITH LONGER PREOPERATIVE STAY

Mohammad Mehdi Houshmandi, Luke Eckersley, Winnie Savard, Deborah S. Fruitman, Lindsay Mills, Lisa K. Hornberger

**Background:** Neonates with critical coarctation of the aorta (CoA) may present in extremis if unrecognized. Prenatal diagnosis permits more appropriate early management of affected neonates.

**Methods:** We retrospectively compared the clinical presentation, preoperative condition and operative course of neonates prenatally (Group 1, G1) or only postnatally (Group 2, G2) diagnosed in Alberta from 2004 to 2015 with critical CoA. Cases with other left heart obstructive lesions and ventricular septal defects were included, but those with more complex heart disease were excluded. Preoperative data analysed included highest lactate and lowest arterial pH, highest creatinine and urea, level of support required (use of inotropes, bicarbonate, oxygen, respiratory support), and pre and postoperative length of hospital stay (LOS).

**Results:** In total, 110 cases were included: G1-44 and G2-66. Age at surgery differed between groups (G1: median 7 [1-30 days] vs G2: 10 [1-30 days] p = 0.05). Preoperatively, G2 had a greater incidence of metabolic acidosis with a pH<7.29 in 5.1% vs 31% (p=0.002) and highest lactate >3.5 mmol/L in 5.3% vs 25.5% (p=0.009) in G1 vs G2, respectively), and need for support including supplemental oxygen (24% vs 48%, G1 vs G2, respectively, p=0.028), and bicarbonate administration (0% vs 5%, G1 vs G2, p=0.001). Need for preoperative ventilation (43% vs 55%, G1 vs G2, respectively) and preop inotrope use (25.7% vs 38%) did not differ between groups. Total LOS was significantly longer in G1 patients (median 19.5 [5-72 days] vs G2 12.5 [4-58 days] p=0.024) which was due to longer preoperative LOS (median 7 [1-22 days] vs 3 [0-25 days], G1 vs G2, respectively p<0.001), as postoperative LOS did not differ.

**Conclusion:** Prenatal diagnosis of critical CoA is associated with improved preoperative condition with reduced metabolic acidosis and need for support; however, it is also associated with longer preoperative hospitalization. The factors responsible for lengthier preoperative stay among prenatally diagnosed cases are currently being explored to determine modifiable factors.
Background: Impaired longitudinal strain in tetralogy of Fallot (TOF) has been associated with adverse clinical outcome. Assessment of myocardial deformation using novel CMR software may provide prognostic information in TOF. We aimed to determine correlates of RV function using TV displacement analysis in patients with repaired TOF.

Methods: A retrospective analysis of 62 CMR studies in patients (14±5 years) with repaired TOF (35 transannular patch, 14 RV-PA conduit, 8 valve-sparing repair, 5 pulmonary valve replacement). Right ventricular volumes and ejection fraction were recorded. Peak RV longitudinal strain and strain rate (SR) were measured from the 4-chamber cine view using in-house developed CMR software that utilizes a semi-automatic feature tracking program. Tricuspid valve (TV) displacement was measured at end-systole as the shortest distance between both anterior and septal leaflet hinge points relative to the RV apex, and the velocity of shortening in systole and early diastole (e') was computed (Figure). Pearson’s correlation coefficient was calculated between RV volumes, RVEF, RV strain, and SR, with TV displacement parameters.

Results: Increased anterior and septal distance (i.e. decreased shortening) was associated with larger RV volumes, decreased RVEF and longitudinal strain; but showed no relationship to SR. Increased anterior displacement velocities were associated with increased longitudinal strain, SR and EDSR, while septal velocity correlated with SR only. Both anterior and septal e’ velocities increased with increasing RVEF, strain, SR and EDSR (Table).

Conclusion: Decreased TV shortening in systole is associated with larger RV volumes and decreased RV function. Greater anterior displacement velocities in systole and early diastole are associated with improved RV function, contractility and early filling rate. TV displacement analysis provides a simple correlate of RV function, and may be a quicker, serial method to estimate RV myocardial mechanics in repaired TOF.
A CLUSTER RANDOMIZED TRIAL OF A TRANSITION INTERVENTION FOR ADOLESCENTS WITH CONGENITAL HEART DISEASE

Andrew Mackie, Gwen Rempel, Adrienne Kovacs, Miriam Kaufman, Ahlexxi Jelen, Kathryn Rankin, Erwin Oechslin, Renee Sananes, Maryna Yaskina, Brian McCrindle

Background: There is little evidence regarding the efficacy of interventions to prepare adolescents with congenital heart disease (CHD) to assume responsibility for their health and self-management upon transfer to adult care.

Methods: We conducted a randomized clinical trial of a nurse-led transition intervention for 16-17 year olds with moderate or complex CHD versus usual care. The intervention group received two 1-hour individualized sessions targeting CHD education and self-management skills. The primary outcome was excess time to adult CHD care, defined as the actual interval between the final pediatric and first adult cardiology appointments, minus the recommended time interval. Secondary outcomes were scores on the MyHeart CHD knowledge survey and Transition Readiness Assessment Questionnaire (TRAQ).

Results: One hundred and twenty-one participants were randomized to intervention (57) or usual care (64). At the recommended time of first adult appointment (excess time=0), intervention participants were 1.8 times more likely to have their appointment within one month (95% CI 1.11-2.86, Cox regression p=0.018). This hazard increased with time; at an excess time of 6 months, intervention participants were 3.0 times more likely to have an appointment within one month (95% CI 1.07 – 8.26). The intervention group had higher scores at 1, 6, 12 and 18 months on both the MyHeart knowledge survey (p<0.001, mixed models) and TRAQ self-management index (p=0.032, mixed models).

Conclusion: A nurse-led intervention reduced the likelihood of a delay in adult CHD care and improved CHD knowledge and self-management skills. A structured intervention program is recommended for all adolescents with CHD.
UMBILICAL ARTERIAL BLOOD FLOW IN THE THIRD TRIMESTER AND ITS ASSOCIATION WITH CLINICAL AND NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH CRITICAL NEONATAL CONGENITAL HEART DISEASE

Jayani Abeysekera, Dora Gyenes, Charlene M.T. Robertson, Gwen Bond, Irina Dinu, Dianne Creighton, Joseph Atallah, Ivan Rebeyka, Lisa K. Hornberger

Background: Children with congenital heart disease are at increased risk of adverse long-term neurodevelopmental outcomes believed in part secondary to a prenatal insult. Altered fetal middle cerebral arterial (MCA) Dopplers suggestive of brain sparing (low Pulsatility Index, PI) as well as placental pathology have been documented in fetal heart disease. In this study, we investigated the relationship between MCA and umbilical arterial, UA, flow patterns in fetal transposition of the great arteries (TGA) and hypoplastic left heart syndrome (HLHS) on growth and 2-year neurodevelopmental outcomes.

Methods: We identified children with d-TGA and HLHS within the Western Canadian Complex Pediatric Therapies Follow-Up Program who had a 3rd trimester fetal echocardiogram between October 2004 and August 2014. Participants with inadequate fetal Doppler data or death prior to 2-year follow-up were excluded. MCA and UA PI measurements were obtained via offline analysis of 3rd trimester fetal echocardiograms. The relationship with birth and 2 year somatic measures, and 2 year Bayley Scales of Infant and Toddler Development III composite scores were analyzed using two-sided Pearson correlations (r).

Results: Children with d-TGA (n=24) and HLHS (n=36) were included. MCA PI did not correlate with birth somatic measures or 2-year neurodevelopmental outcomes. UA PI, however, inversely correlated birth and 2 year head circumference (r=-0.36, p=0.005 and r=-0.25, p=0.05), length (r=-0.27, p=0.039 and r=-0.40, p=0.001) and weight (r=-0.31, p=0.015 and r=-0.44, p=0.001), and 2-year cognitive (r=-0.30, p=0.019), language (r=-0.30, p=0.022) and motor scores (r=-0.27, p=0.04).

Conclusions: A higher UA PI, suggestive of placental insufficiency, in fetal HLHS and d-TGA is associated with worse 2-year growth and neurodevelopmental outcomes. This could represent an additional insult that contributes to long-term outcomes in critical neonatal heart disease. Understanding these risk factors allows for early identification and intervention to ultimately improve outcomes and decrease disease burden.
EXTERNAL VALIDATION AND IMPROVEMENT OF EHMRRG RISK MODEL USING A POPULATION-BASED COHORT OF PATIENTS WITH HEART FAILURE

Nariman Sepehrvand, Erik Youngson, Jeffrey A. Bakal, Finlay A. McAlister, Brian H. Rowe, Justin A. Ezekowitz

**Background:** Emergency Heart Failure Mortality Risk Grade (EHMRRG) is a 10-item risk score that was developed to assess the risk of dying in the next 7 days for patients with acute heart failure (AHF) in the emergency department (ED). However, it lacks key variables including natriuretic peptide (NP) values and widely used triage scores.

**Purpose:** We aimed to externally validate and refine the EHMRRG risk model using a cohort of patients who presented to ED via ambulance with AHF.

**Methods:** Cohort study using administrative data of all ambulance-transported patients from Alberta (2012 - 2016) presenting to the ED with a primary diagnosis of acute HF (ICD-10 I50.x). Data were linked to laboratory data for EHMRRG variables; Canadian Triage & Acuity Scale (CTAS) was available for all patients in urban and regional centres. The C-index and Net reclassification improvement (NRI) were used to assess overall model quality.

**Results:** The cohort consisted of 6,708 patients with AHF. The 7-day mortality was 0.9%, 2.8%, 4.2%, 4.6%, and 13.3%, across the 1st to 5th quintiles. The EHMRRG score had a c-index of 0.73 (95%CI 0.71 to 0.76) and 0.71 (95%CI 0.70 to 0.73) for identifying patients at risk of 7-day and 30-day mortality. Addition of NP (BNP or NT-proBNP) to the EHMRRG model improved the net re-classification index of patients (p<0.01) for 7-day mortality as did the addition of the CTAS (p<0.02). The EHMRRG model had a reduced discriminatory performance without inclusion of the troponin component with an NRI of -0.27 (95%CI -0.36 to -0.17, p<0.01) for predicting 7-day mortality. There was no association between the use of metolazone and 7-day mortality, and its removal did not alter the model's predictive ability (p=0.9).

**Conclusion:** The EHMRRG model exhibited moderate discriminative ability in a large population-based cohort of patients with HF in the ED. Revision of the EHMRRG score through factor inclusion (NPs; triage scores) and exclusion (metolazone) could improve the model's performance and should be incorporated into future studies of the model.

**Table.** EHMRRG model performance in predicting 7-day death

<table>
<thead>
<tr>
<th>Variables included in model</th>
<th>C-index (95% CI)</th>
<th>P-value for C-index difference</th>
<th>NRI (95% CI)</th>
<th>NRI P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EHMRRG variables</td>
<td>0.75 (0.72 to 0.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ BNP / NT-proBNP</td>
<td>0.76 (0.73 to 0.78)</td>
<td>&lt;0.01</td>
<td>0.27 (0.17 to 0.36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EHMRRG + BNP / NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ CTAS</td>
<td>0.77 (0.74 to 0.79)</td>
<td>&lt;0.01</td>
<td>0.13 (0.02 to 0.23)</td>
<td>0.02</td>
</tr>
<tr>
<td>EHMRRG excl. Troponin</td>
<td>0.74 (0.71 to 0.76)</td>
<td>0.02</td>
<td>-0.27 (-0.36 to -0.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EHMRRG excl. Metolazone</td>
<td>0.75 (0.72 to 0.77)</td>
<td>0.5</td>
<td>0.00 (-0.08 to 0.07)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

BNP: B-type natriuretic peptide; CTAS: Canadian Triage and Acuity Scale; ED: emergency department; EHMRRG: the Emergency Heart Failure Mortality Risk Grade; NRI: net reclassification improvement; NT-proBNP: amino-terminal proBNP;
CHF-CLIN-2

HOME OR HOSPITAL? TRENDS AND PREDICTORS OF LOCATION OF DEATH AMONG PATIENTS WITH HEART FAILURE AND ACUTE CORONARY SYNDROMES

Xi (Jacksy) Zhao, Justin A. Ezekowitz, Anamaria Savu, Finlay A. McAlister, Robert C. Welsh, Kevin R. Bainey, Paul W. Armstrong, Padma Kaul

Background: Cardiovascular disease (CVD) accounts for a third of all deaths in Canadian adults. Little is known about the proportion of patients with heart failure (HF) that die at home and how this differs from patients with acute CVD such as acute coronary syndromes (ACS). We examined temporal trends and patient factors associated with location of death over 5 years following hospitalization for ACS or HF in Alberta, Canada.

Methods: Our study included all patients discharged alive from a hospitalization with a primary diagnosis of HF (n = 30279) or ACS (n = 55515) between April 1, 2002 and March 31, 2014 in Alberta, Canada. The first hospitalization during the study period was used as the index. The location of death was categorized as home (out of hospital, OOH), non-acute care hospital or acute care hospital (which included the emergency department).

Results: In the HF cohort, 39%, 38%, and 40% of deaths occurred OOH at 90 days, 1 year, and 5 years post-discharge, respectively. In the ACS cohort, 30%, 33%, and 39% of deaths occurred OOH at 90 days, 1 year, and 5 years post-discharge, respectively. Younger age and urban residence were associated with a higher likelihood of OOH death. Among patients with HF, the pattern of OOH death did not change between 2002 and 2013. In patients with ACS, there was a trend toward fewer OOH deaths in the 1 year post-discharge group from 2002 and 2012.

Conclusion: Approximately 40% of deaths after HF or ACS hospitalizations occur OOH. The reasons for the sustained high proportion of acute care hospital deaths in patients with HF require further investigation.
Figure 1: Comparison of location of death at 90 days, 1 year and 5 years post-discharge from HF and ACS hospitalizations

A. 90 days post-discharge

B. 1 year post-discharge

C. 5 years post-discharge

Legend:
- Acute hospital
- Non-acute Hospital
- Emergency Department
- Out of Hospital
Background: Anabolic-androgenic steroid (AAS) abuse has increased in recent years where they have been linked to adverse cardiovascular effects. Left ventricular assist device (LVAD) therapy may be an important intervention for bridging to heart transplant candidacy, recovery, or destination therapy. We report a case of severe cardiomyopathy likely secondary from AAS abuse that was managed with implantation of a HeartMate II LVAD (Abbott Laboratories, Abbott Park, IL) with successful recovery of heart function to allow for LVAD discontinuation.

Methods: A 26-year-old previously healthy man with a history of AAS abuse presented to the emergency department with shortness of breath, hemoptysis and a presumed diagnosis of worsening pneumonia resistant to antibacterial treatment. Computed tomography of the chest revealed bilateral extensive airspace opacities. Echocardiography revealed an estimated left ventricular ejection fraction (LVEF) <10%. A severely dilated and impaired left ventricle and mildly dilated right ventricle were confirmed with MRI. He deteriorated rapidly with hemodynamic compromise requiring urgent circulatory support.

Results: Given his critical condition, substance abuse and uncertainty of his ability to abstain from substances, he was deemed unsuitable for transplantation at this time. A HeartMate II LVAD was implanted as a bridge to candidacy, recovery or as destination therapy. LVAD core pathology revealed cardiomyocyte hypertrophy, patchy myocyte death and histiocytic inflammatory reaction consistent with AAS induced heart failure. Postoperatively, he was discharged home, connected with addictions counseling, rehabilitation and heart failure therapy. Following 18 months in the community on LVAD support, there was demonstration of recovery in ventricular function with a LVEF of 55% (vs. initial <10%), left ventricular internal diameter end diastole 4.2 cm (vs. initial 7.4 cm) and systole of 2.6 cm (vs. initial 6.9 cm). With a subsequent weaning trial demonstrating good hemodynamic and functional parameters, a decision was made to proceed with device discontinuation. Rather than a definitive LVAD explantation and to minimize trauma to the recovered myocardium, the LVAD was discontinued by removing the driveline in its entirety and occluding the outflow graft. This allowed the device to be left in-situ and leaves a natural orifice to re-implant a new device at a later date should that be necessary with recurrence of heart failure in the long-term. Heart function remained excellent post-LVAD discontinuation (LVEF >60%) and the patient was discharged on POD 7 on full heart failure management.

Conclusion: The present report demonstrates that severe cardiomyopathy likely secondary from AAS abuse can be successfully supported with a durable LVAD with excellent recovery of ventricular function. Our report also highlights that AAS use should be considered in the differential diagnosis of left ventricular systolic dysfunction. Improved education and awareness of complications of AAS may lead to better recognition and prompt treatment of their potentially lethal effects.
IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE REALLY A RISK FACTOR FOR CORONARY ARTERY DISEASE?
Yongzhe Hong, Michelle Graham, M. Sean McMurtry

**Background:** Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) are leading causes of morbidity and mortality. Smoking causes COPD and CAD, but whether COPD is an independent risk factor for CAD is unknown. We sought to test for an association between COPD and angiographic CAD after adjusting for risk factors including smoking.

**Methods:** We obtained data from The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH). APPROACH is a prospective registry capturing all patients undergoing cardiac intervention and revascularization in the province of Alberta, Canada, since 1995. We included patients age > 18 years who had undergone coronary angiogram between April 1, 2007 and March 31, 2014. A patient was considered to have coronary heart disease if at least one coronary artery has a significant stenosis ≥ 50%. COPD was presented if the patient has a documented history and was on a pharmacological therapy. We performed multivariate logistic regression to evaluate the association between CAD and COPD.

**Results:** There were 26,137 patients included in the analysis, with a mean age of 63.3 ± 12.2 years and 19,542 (74.8%) of which were male. The crude odds ratio of having CAD was 0.83 (95% CI 0.74-0.92) for patients with COPD compared to those without COPD in univariate logistic regression analysis. After controlling for age, gender, smoking history, BMI and hypertension, diabetes, hyperlipidemia, peripheral artery disease, and cardiac family history it became 0.75 (95% CI 0.67-0.84).

**Conclusion:** Patients with COPD were associated with a reduced risk of CAD in patients referred for coronary angiography, after adjustment for risk factors. COPD is not an independent risk factor for CAD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>[0.74, 0.92]</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.75</td>
<td>&lt;0.001</td>
<td>[0.67, 0.84]</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.01</td>
<td>&lt;0.001</td>
<td>[1.01, 1.02]</td>
</tr>
<tr>
<td>Men</td>
<td>1.77</td>
<td>&lt;0.001</td>
<td>[1.62, 1.92]</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.15</td>
<td>0.001</td>
<td>[1.05, 1.24]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.41</td>
<td>&lt;0.001</td>
<td>[1.28, 1.56]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.96</td>
<td>0.352</td>
<td>[0.88, 1.04]</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.96</td>
<td>0.296</td>
<td>[0.88, 1.04]</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>1.46</td>
<td>&lt;0.001</td>
<td>[1.26, 1.70]</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.283</td>
<td>[0.99, 1.01]</td>
</tr>
<tr>
<td>Family history of heart attacks</td>
<td>1.31</td>
<td>0.408</td>
<td>[0.95, 1.12]</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; BMI, body mass index.
SAFETY OUTCOMES WITH ANESTHESIOLOGIST DIRECTED SEDATION COMPARED TO NON-ANESTHESIOLOGIST FOR DEFIBRILLATION THRESHOLD TESTING

Kenneth K Quadros, Roopinder K Sandhu, Stuart J. Connolly, Michael Glikson, Valentina Kutyifa, Phillippe Mabo, Stefan Hohnloser, Gilles O’Hara, Liselot VanErven, Jorg Neuzner, Josef Kautzner, Frederik Gadler, Xavier Vinolas, Ursula Appl, Yan Yun Liu, Jeff S. Healey

Background: No standard practice exists with respect to anesthesiologist directed sedation (ADS) versus administration by non-anesthesiology (Non-ADS) for defibrillation threshold (DT) testing. Our objective was to evaluate adverse events and safety outcomes with ADS compared to non-ADS for DT testing.

Methods: A sub-study analysis of the Shockless Implant Evaluation (SIMPLE) study was performed among the 1242 patients who had DT testing (624 with ADS and 618 with non-ADS). We determined composite in-hospital adverse events, composite intraoperative safety outcomes and two predefined composite safety outcomes at 30 days from the main trial (Table 1). Logistic regression models and cox hazard models were used to estimate odds ratios (OR, 95%CI) and hazard ratios (HR, 95%CI) respectively for outcomes and method of sedation.

Results: Compared to non-ADS, patients who received ADS were more likely to be younger (62 years vs. 64 years, p=0.01), have lower ejection fraction (EF 0.31vs. 0.33, p=0.03), receive inhalational anesthesia, propofol, narcotics (p<.001, respectively) and have an arterial line (43% vs.8%, p<.0001). Independent predictors associated with ADS sedation were presence of coronary artery disease (OR 1.69, 95% CI 1.0-2.72, p=0.03) and hypertrophic cardiomyopathy (OR 2.64, 95% CI 1.19- 5.85, p=0.02). Patients in the ADS group had a higher composite intraoperative safety event outcome (2.2% vs 0.5%; HR 4.70, 95% CI 1.35-16.5, p=0.02) and primary composite safety outcome at 30 days (8.2% vs 4.9%; HR 1.70 95% CI 1.08-2.67 p=0.02) compared to the non-ADS group (Table 1).

Conclusion: Sedation for DT testing by non-anesthesiologists is safe. Complications were higher among patients having ADS; however, this is likely the result of selection bias.
THE ASSOCIATION BETWEEN APICAL PERIODONTITIS AND CARDIOVASCULAR DISEASE: SYSTEMATIC REVIEW

Yuli Berlin-Broner, Maria Febbraio, Liran Levin

**Background:** A systematic review was conducted to assess the association between apical periodontitis (AP) and cardiovascular disease (CVD).

**Methods:** Studies published from the earliest date available until September 2015 were retrieved from the Medline, PubMed and Embase databases. The included studies reported the results from observational studies and assessed the link between AP and CVD as confirmed by one of the following criteria: diagnosed coronary artery disease, angina pectoris, acute myocardial infarction, stroke, or mortality caused by cardiac pathology. Independent researchers following the PRISMA standard protocol abstracted the study characteristics. NOS criteria were used to rate the quality of the studies and the GRADE was used for level of evidence evaluation.

**Results:** Nineteen epidemiological studies fulfilled the pre-determined inclusion criteria: 10 case-control studies, 5 cross-sectional studies and 4 cohort studies. There was considerable heterogeneity among the included studies in terms of their study design, population, outcomes of interest and AP evaluation methods. Considering the limited availability and the heterogeneity among the studies, meta-analysis was not attempted. Thirteen of the 19 included studies found a significant positive association between apical periodontitis and cardiovascular disease, although in 2 of them the significance was present only in univariate analysis. Five studies failed to reveal positive significance, and one study reported a negative association.

**Conclusion:** Although most of the published studies found a positive association between apical periodontitis and cardiovascular disease, the quality of the existing evidence is moderate-low and a causal relationship cannot be established.
IHD-CLIN-1

COMPARATIVE EFFICACY AND BLEEDING OUTCOMES AMONG P2Y12 INHIBITORS IN ST ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION; INSIGHTS FROM THE TOTAL TRIAL

Robinder Sidhu, John Cairns, Shahar Lavi, Sasko Kedev, Raul Moreno, Warren Cantor, Goran Stankovic, Brandi Meeks, Fei Yuan, Vladimir Dzavik, Sanjit Jolly, Robert Welsh

Background: Primary percutaneous coronary intervention (PPCI) with adjunctive medical therapy including dual anti-platelet therapy, aspirin and P2Y12 receptor inhibitor, is standard of care for ST elevation myocardial infarction (STEMI). Neither the TRITON-TIMI 38 (Prasugrel) nor PLATO (Ticagrelor) trials enrolled a large cohort of STEMI patented receiving expedited PPCI. Thus comparison across all three agents is limited, leaving an important knowledge gap in STEMI.

Methods: The TOTAL trial (ThrOmbectomy with PCI versus PCI ALone in patients with STEMI undergoing primary PCI) randomized 10,02 patients. For this post hoc analysis, patients were grouped based on P2Y12 inhibitor use: Clopidogrel (C) (n=6310), Prasugrel (P) (n=1195), or Ticagrelor (T)(n=2014). The primary outcome was the one year composite of CV death, recurrent MI, cardiogenic shock, or NYHA Class IV heart failure. Cox proportional hazard models were used and adjusted for confounders using propensity scoring. Secondary efficacy and safety outcomes were also assessed.

Results: Baseline characteristics were similar between groups with the exception that Prasugrel patients were less likely to be >75yo (P5.5%, C14.5%, T11.6%) or have prior stroke (P0.7%, C3.7%, T2.2%) but had higher rates of diabetes (P20.3%, C18.8%, T15.2%). After adjustment, Prasugrel use was not associated with a reduction in the primary outcome compared to Clopidogrel (aHR 1.03; 95%CI=0.82 – 1.30, p = 0.81). Ticagrelor use reduced the primary composite outcome when compared to both Clopidogrel (aHR 0.64; 95% CI=0.51-0.79, p < 0.001) and Prasugrel (aHR 0.63; 95% CI=0.46-0.85, p = 0.002). Neither Prasugrel nor Ticagrelor were associated with increased bleeding or stroke compared to Clopidogrel.

Conclusion: In STEMI undergoing PPCI, ticagrelor was associated with a significantly lower rate of the composite outcome 1 year without increasing bleeding or stroke risk. Comparatively, prasugrel offered no definite advantage over clopidogrel in this population. This adjusted post-hoc analysis supports the use of ticagrelor over either clopidogrel or prasugrel in the setting of STEMI undergoing PPCI.
FACTORS INFLUENCING AMBULANCE USE IN PATIENTS WITH SUSPECTED ACUTE CORONARY SYNDROMES: A POPULATION-BASED GEOGRAPHIC INFORMATION SYSTEM STUDY

Nariman Sepehrvand, Wendimagegn Alemayehu, Padma Kaul, Rick Pelletier, Aminu K. Bello, Robert C. Welsh, Paul W. Armstrong, Justin A. Ezekowitz

Background: Despite all public awareness campaigns and guideline recommendations, the majority of patients with symptoms suggestive of acute coronary syndrome (ACS) do not use emergency medical services (EMS) to reach the emergency department (ED).

Purpose: The aim of this study was to investigate the factors associated with EMS utilization and subsequent patient outcomes.

Methods: We used data from the metropolitan areas of Edmonton and Calgary, which are of similar size and in the same public health system (population ~3 million people). Using administrative health databases, all patients who presented to an ED in the years of 2007-2013 with main ED diagnosis of ACS, stable angina or chest pain were included. The travel distance was estimated using the geographic information system method to approximate distance between ED and patient home. The clinical endpoints of interest were the 7-day and 30-day all-cause events (composite of death, re-hospitalization, and repeat ED visit).

Results: The cohort consisted of 50,881 patients, 15,553 (30.5%) of which were presented via EMS. The overall rate of EMS utilization was lower in Edmonton compared to Calgary (24.2% vs 36.2%; p<0.0001). Based on multivariate analysis, patients with older age, female sex, ED diagnosis of ACS and stable angina (as compared to chest pain), more comorbidities, with longer travel distance and lower household income were more likely to use EMS to reach the hospital. After adjustment for covariates and with propensity analysis/IPW, EMS use was associated with higher risk of 7-day (OR=1.17, 95%CI 1.09-1.25) and 30-day (OR=1.20, 95%CI 1.13-1.27) clinical events.

Conclusion: Several demographic and clinical features were associated with higher EMS use including geographic variation. This has implications for the design of EMS systems, triage and early diagnosis and treatment options.
**Figure.** Factors associated with the mode of ED presentation (EMS versus self-transport)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 yr</td>
<td></td>
</tr>
<tr>
<td>≤65 years</td>
<td>1.25 (1.23-1.28)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>2.09 (2.02-2.16)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.15 (1.10-1.20)</td>
</tr>
<tr>
<td>ED Diagnosis</td>
<td></td>
</tr>
<tr>
<td>CP/CP-NOS</td>
<td>Ref</td>
</tr>
<tr>
<td>Stable angina</td>
<td>1.28 (1.15-1.45)</td>
</tr>
<tr>
<td>Non-STE ACS</td>
<td>1.38 (1.27-1.49)</td>
</tr>
<tr>
<td>STEMI</td>
<td>3.09 (2.63-3.62)</td>
</tr>
<tr>
<td>Metro residence</td>
<td></td>
</tr>
<tr>
<td>Calgary</td>
<td>Ref</td>
</tr>
<tr>
<td>Edmonton</td>
<td>0.54 (0.45-0.64)</td>
</tr>
<tr>
<td>Day of the week</td>
<td></td>
</tr>
<tr>
<td>Monday-Friday</td>
<td>Ref</td>
</tr>
<tr>
<td>Weekend</td>
<td>1.09 (1.04-1.14)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>1.11 (1.01-1.21)</td>
</tr>
<tr>
<td>HF</td>
<td>1.30 (1.12-1.51)</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>1.32 (1.09-1.60)</td>
</tr>
<tr>
<td>Dementia</td>
<td>2.73 (1.96-3.81)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.47 (1.29-1.67)</td>
</tr>
<tr>
<td>A.Fib</td>
<td>1.18 (1.00-1.39)</td>
</tr>
<tr>
<td>Driving distance, per Km</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.99 (1.09-1.10)</td>
</tr>
<tr>
<td>Household Income, per $10,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.83 (0.82-0.84)</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; A.Fib: atrial fibrillation; COPD: chronic obstructive pulmonary disease; CP: chest pain; CP-NOS: chest pain-not otherwise specified; ED: emergency department; EMS: emergency medical services; HF: heart failure; HTN: hypertension; SA: stable angina; STEMI: ST segment elevation myocardial infarction;
IHD-CLIN-3

TRENDS IN CAUSE-SPECIFIC MORTALITY AFTER PERCUTANEOUS CORONARY INTERVENTION (PCI): OBSERVATIONS FROM THE ALBERTA PROVINCIAL PROJECT FOR OUTCOME ASSESSMENT IN CORONARY HEART DISEASE (APPROACH) REGISTRY

Walid Barake, Dat Tran, Diane Galbraith, Colleen Norris, Merrill L Knudtson, Padma Kaul, Finlay A. McAlister, Roopinder K Sandhu

Background: Percutaneous coronary intervention (PCI) patients are reportedly now older with higher comorbidity burdens yet little is known about the impact on cause-specific mortality.

The aim of the study was to describe trends in 30-day, 1-, and 2-year cause-specific mortality and the contribution of cardiac and non-cardiac causes of long-term mortality in a large, contemporary cohort undergoing PCI.

Methods: We used the APPROACH registry (Alberta Provincial Project for Outcome assessment in Coronary Heart disease) which captures demographics, clinical and angiographic data on all patients undergoing coronary angiograms in Alberta, Canada to identify consecutive patients > 20 years undergoing their first PCI from 2005-2013. Causes of death were classified into cardiac or non-cardiac based on judgement of each patient’s attending physician.

Results: Of the total 35, 602 patients who underwent PCI, 5284 (14.8%) died. Over time, patients were older, had more cardiovascular comorbidities (but not more non-cardiovascular comorbidities) and more PCIs were done for an indication of acute coronary syndrome and less for stable angina. The 30-day, 1-year, and 2-year total and cardiac mortality after PCI increased significantly over the 9 years’ studies, while non-cardiac mortality remained unchanged over the years. The most common cause of death was cardiac at 30-day, 1-, and 2-years but non-cardiac deaths increased 28% as time from PCI increased (proportion of deaths were cardiac: 30 days=82.5%, 1 year= 63.9%, 2 years=55%; non-cardiac: 30 days=11.8%, 1 year=31.9%, 2 years=39.9%; p for trend=<.001). The major drivers for these opposite trends were fewer fatal myocardial infarctions (76.6% to 53.9%, p <0.001) and more deaths resulting from lung neoplasms (6.5% to 11.3% p=0.03). Cause-specific mortality shifted after 4 years post-PCI with non-cardiac deaths predominating.

Conclusion: In this real-world registry, as clinical profiles of patients undergoing PCI are changing, total and cardiac mortality are increasing. The primary contributor to short-term mortality is cardiac but by 4 years post-PCI non-cardiac mortality predominates.
Figure 1: Cumulative mortality from the last PCI by mode of death

<table>
<thead>
<tr>
<th>Time to death (years)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause (%)</td>
<td>0.6</td>
<td>4.5</td>
<td>6.3</td>
<td>8.0</td>
<td>9.6</td>
<td>11.0</td>
<td>12.2</td>
<td>13.1</td>
<td>13.9</td>
<td>14.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Cardiac Death (%)</td>
<td>0.5</td>
<td>2.9</td>
<td>3.5</td>
<td>4.0</td>
<td>4.4</td>
<td>4.9</td>
<td>5.2</td>
<td>5.5</td>
<td>5.7</td>
<td>5.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Non-cardiac Death (%)</td>
<td>0.0</td>
<td>1.4</td>
<td>2.5</td>
<td>3.5</td>
<td>4.5</td>
<td>5.2</td>
<td>5.8</td>
<td>6.3</td>
<td>6.7</td>
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<td>2007</td>
<td>2008</td>
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<td>% patient</td>
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<td>3.618</td>
<td>3.821</td>
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<td>(11.9)</td>
<td>62.2</td>
<td>(11.9)</td>
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<td>(11.9)</td>
<td>62.5</td>
<td>(11.9)</td>
<td>62.7</td>
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<td>(54-70)</td>
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<td>(54-71)</td>
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<td>Female (%)</td>
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<td>23.9</td>
<td>23</td>
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<td>69.9</td>
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<td>&lt;0.001</td>
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<td>25.9</td>
<td>23.9</td>
<td>24.5</td>
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<td>26</td>
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<td>24.9</td>
<td>26.5</td>
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<td>5.9</td>
<td>4.2</td>
<td>4.2</td>
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<td>7.2</td>
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<td>5.8</td>
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<td>11.6</td>
<td>11.7</td>
<td>12.4</td>
<td>11.3</td>
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<td>Peripheral vascular disease</td>
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<td>Non-cardiac Comorbidities (%)</td>
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<td>Malignancy</td>
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<td>3.2</td>
<td>3.2</td>
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<td>0.7</td>
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<td>0.7</td>
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<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5.1</td>
<td>5</td>
<td>5.9</td>
<td>6.1</td>
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<td>5.2</td>
<td>5.1</td>
<td>5.1</td>
<td>4.4</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Repeat PCI within 90 days</td>
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<td>7.7</td>
<td>7.1</td>
<td>7.2</td>
<td>7.2</td>
<td>7.7</td>
<td>8.8</td>
<td>9.5</td>
<td>8.9</td>
<td>0.001</td>
<td></td>
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<tr>
<td>History of smoking (%)</td>
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<td>34.2</td>
<td>36.9</td>
<td>38.1</td>
<td>37.5</td>
<td>37.8</td>
<td>37</td>
<td>40</td>
<td>42.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Current                          | 32.8  | 36.7  | 33.3  | 33.9  | 31.3  | 32.6  | 34    | 31    | 32.7  | 31    | 0.980  |
| Fos                            | 29.9  | 39.3  | 32.5  | 29.2  | 28.6  | 29.8  | 27.9  | 29    | 27.3  | 26.3   | <0.001 |
| Indication for catheterization (%) |       |       |       |       |       |       |       |       |       |       |         |
| STEMI                           | 33    | 36.7  | 31.2  | 32.9  | 32.2  | 32.4  | 34    | 34.3  | 34.8  | 34.1   | <0.001 |
| NSTEMI                          | 28.6  | 26.3  | 27.8  | 30.2  | 29.8  | 29.6  | 28.6  | 30.3  | 29.9  | 30.8   | <0.001 |
| Unstable Angina                 | 12    | 15.6  | 13.7  | 11.6  | 12.6  | 12    | 11.2  | 10.2  | 10.3  | 10.8   | <0.001 |
| Stable Angina                   | 20.3  | 21.3  | 21.8  | 18.8  | 20    | 21.2  | 20.6  | 20.5  | 19.3  | 19.4   | 0.019  |
| Other                           | 6.1   | 12.1  | 5.5   | 6.5   | 5.5   | 4.8   | 5.5   | 4.8   | 5.7   | 4.9    | <0.001 |
| Total mortality (%)             |       |       |       |       |       |       |       |       |       |       |         |
| 30-day                          | 2.1   | 1.5   | 1.8   | 2.1   | 2.1   | 1.9   | 2.6   | 2.3   | 2     | 2.7    | 0.001  |
| 1-year                          | 4.2   | 3.3   | 3.6   | 3.9   | 4.1   | 3.9   | 4.8   | 4.5   | 4.3   | 3.1    | <0.001 |
| 2-year                          | 6     | 5.2   | 5.1   | 5.6   | 5.6   | 6.1   | 6.7   | 6     | 6.3   | 6.9    | <0.001 |
| Cardiac mortality (%)           |       |       |       |       |       |       |       |       |       |       |         |
| 30-day                          | 1.8   | 1.2   | 1.6   | 1.7   | 1.8   | 1.6   | 2.1   | 1.8   | 1.6   | 2.4    | 0.001  |
| 1-year                          | 2.7   | 1.8   | 2.5   | 2.4   | 2.6   | 2.3   | 3.1   | 2.7   | 2.6   | 3.6    | <0.001 |
| 2-year                          | 3.3   | 2.8   | 3.1   | 3     | 3.1   | 3.2   | 3.9   | 3.4   | 3.2   | 4.2    | <0.001 |
| Non-cardiac mortality (%)       |       |       |       |       |       |       |       |       |       |       |         |
| 30-day                          | 0.3   | 0.3   | 0.2   | 0.2   | 0.2   | 0.3   | 0.3   | 0.3   | 0.3   | 0.2    | 0.684  |
| 1-year                          | 1.3   | 1.3   | 1     | 1.3   | 1.4   | 1.4   | 1.6   | 1.5   | 1.3   | 1.3    | 0.183  |
| 2-year                          | 2.4   | 2.3   | 1.9   | 2.3   | 2.3   | 2.7   | 2.5   | 2.5   | 2.7   | 2      | 0.531  |
IHD-CLIN-4

MYOCARDIAL ISCHEMIA AND MOBILIZATION OF CIRCULATING PROGENITOR CELLS


Background: Circulating progenitor cells (PCs) are involved in vascular repair and regeneration. Low levels of PCs in patients with CAD have been linked to adverse cardiovascular outcomes. The response of PCs to transient myocardial ischemia in patients with CAD remains unknown. We aimed to investigate the PC response to exercise-induced myocardial ischemia (demand ischemia), and compared it to the PC response in patients submitted to pharmacological stress testing.

Methods: 566 patients with stable CAD underwent 99mTc sestamibi myocardial perfusion imaging during exercise (69%) or pharmacological stress (31%). Ischemia was defined as a new or worsening impairment in myocardial perfusion using a 17-segment model. CD34+ and CD34+/CXCR4+ PCs were enumerated by flow cytometry at rest and 45 min after stress testing. Change in PC count was compared between patients with and without myocardial ischemia using mixed linear models.

Results: Mean age was 63±9 years, and 76% were males. The incidence of myocardial ischemia was 31% and 41% during exercise and pharmacological stress test, respectively. Patients with myocardial ischemia during exercise stress had a significant decrease in CD34+/CXCR4+ (-18% vs +14.7%, p=0.001) 45-minutes after stress testing that was inversely correlated with the magnitude of myocardial ischemia (r=-0.19, p=0.003), suggesting a greater reduction in circulating PCs in those with a greater ischemic burden. In contrast, patients who underwent pharmacological stress testing had no change in CD34+/CXCR4+ PCs. Plasma VEGF levels increased post stress in all patients undergoing exercise stress testing.

Conclusion: Exercise-induced myocardial ischemia is associated with a decrease in circulating CD34+/CXCR4+ PCs despite an increase in VEGF levels that cause an increase in circulating PCs in patients without exercise induced ischemia. This decrease may be due to increased homing to the ischemic myocardium. Whether this uptake in PCs has physiologic, therapeutic or prognostic implications needs further investigation.
3D ECHOCARDIOGRAPHY FUSION USING ULTRASOUND CONFIDENCE MAPS

R.H. Abhilash, Michelle Noga, Pierre Boulanger, Harald Becher, Kumaradevan Punithakumar

Background: 3D echocardiography provides accurate, high-quality visualization of the heart and is commonly used for volumetric measurements such as the left ventricular (LV) ejection fraction. Limited field-of-view (FOV) is a commonly accepted limitation of 3D echocardiography when compared to modalities like cardiac MRI and CT. Image fusion techniques help to improve the field-of-view by combining multiple 3D ultrasound scans of the heart taken from different positions and probe orientations. We use an optical tracking technique for echocardiography fusion which is independent of image quality and does not require spatial overlap. It is well known in ultrasound imaging that edges in structures orthogonal to the ultrasound (US) beam reflect the sound waves better and hence have higher image quality. We use this information to create an ultrasound confidence map (UCM) for each pixel location in the fused image. We proposed a new generalized random walker framework (GRW) for echocardiography fusion in which the ultrasound confidence map was incorporated as an edge weight.

Methods: For this study, we acquired 18 three-dimensional ultrasound (3DUS) volume pairs of echocardiography data from 6 healthy volunteers using a Philips iE33 ultrasound scanner (Philips Healthcare, Best, the Netherlands) with an X3-1 matrix array transducer. The position of the transducer was tracked using optical markers located using the Optitrack (NaturalPoint Inc, Corvallis, OR, USA) optical tracking system. The transducer positions were used to align ultrasound volumes scanned at different locations. The pixel intensities in the overlapping regions were determined using a random walker formulation in which pixels were weighted based on values of 1) an ultrasound confidence map (UCM) and 2) a vesselness filter which detected ridge-like structures in the image.

Results: We compared our technique to commonly used fusion techniques such as average fusion (AVG), maximum fusion (MAX) and wavelet fusion (WAV) using quantitative image quality measures such as Contrast to Noise Ratio (CNR), Signal to Noise Ratio (SNR), Wang-Bovik metric and Piella metric. Manually segmented regions in the myocardium, leaflets and bloodpool were used as regions of interest to compute these measures. The proposed GRW framework showed statistically significant (p < 0.01) increase in all these measures with values of CNR = 0.85 ± 0.03, SNR = 7.42 ± 1.98, Wang-Bovik metric = 0.80 ± 0.15 and Piella metric = 0.82 ± 0.01. Upon visual inspection, our fusion technique had the lowest amount of stitching and pixelation artifacts in the blood pool region.

Conclusion: A new approach for echocardiography fusion based on GRW formulation was described. The method incorporated transducer characteristics and image features into the fusion and showed higher values for various image quality metrics when compared to prevalent fusion techniques and reduced pixelation or stitching artifacts. This technique could add substantial value to diagnostic echocardiography.
SEMI-AUTOMATIC VOLUMETRIC ECHOCARDIOGRAPHY SEGMENTATION

Deepa Krishnaswamy, Abhilash Hareendranathan, Michelle Noga, Harald Becher, Kumaradevan Punithakumar

**Background:** In echocardiography, cardiac motion can be assessed by manually drawing contours. The contours, delineating the endocardium and epicardium, can be used to perform 3D volumetric segmentation of the left ventricle (LV). Regional analysis can also be performed, in order to calculate metrics such as stroke volume and ejection fraction. The process of manually delineating contours is time-consuming and may result in inaccuracies depending on the software used, and differences in contour tracing methods.

The goal is to develop a fast, accurate, semi-automated process for 3D volumetric segmentation of the left ventricle. This will decrease the time spent by physicians and improve the reproducibility of subsequent clinical measurements.

**Methods:** Two points are manually selected that define an axis through the left ventricle. Radial slices with equal angular spacing are generated that pass through the axis. A contour is drawn on one slice, and a registration approach (Punithakumar et al. 2015) is used to automatically generate contours on subsequent slices. With two selected points and one manually drawn contour, a 3D volume of a chamber of the heart can be segmented.

**Results:** The proposed approach has been evaluated using a heart phantom (Shelley Medical Imaging Technologies). The dataset was acquired on a Philips iE33 ultrasound scanner using an X3-1 matrix array transducer. Comparing the automated contours to the manually traced contours over all slices, the method yielded an average Dice score of 0.917 with a standard deviation of 0.031. Figure 1 shows the difference between the automated contours in red and the manually traced contours in green for the segmentation of the left ventricle of the phantom.

**Conclusion:** The pilot study demonstrates that a semi-automated method with minimal user input can be used for volumetric segmentation of 3D echocardiography data. Future work includes testing the method on other cardiac chambers, using patient data, and extending the approach to perform segmentation over dynamic 3D echocardiography data.
Background: Cardiac magnetic resonance (CMR) images are useful in assessment of patients with congenital heart disease. Radiologists and cardiologists will use contours (e.g. endocardium and epicardium) to track the motion of the heart through the cardiac cycle. We have developed a software that allows for computing contours for the entire cardiac cycle semi-automatically, given a manual contour. These contours are utilized for generating clinical measurements such as ejection fraction and maximum circumferential strain.

Methods: Using the Python programming language, the PyQT Library, and the VTK Library we have developed a program that allows radiologists to conduct the analysis and generate measurements with minimal user input. This study focuses on improving the user interface and extending the program's ability to perform regional right ventricular analysis. The proposed approach relies on a nonrigid registration algorithm which provides point correspondence between a sequence of CMR images. Given a manual contour on a frame, the proposed approach computes contours in the remaining images in the sequence automatically.

Results: We developed tools to allow the user to control the size of the image, step through frames, play through the cardiac cycle and more. Multiple series can be loaded at one time allowing the physicians to analyze many different scans at once. The program is capable of loading hundreds of images within a few seconds. The program has been tested by several users on many different data sets which includes patients with hypoplastic left heart syndrome and tetralogy of Fallot and it is robust enough to yield accurate results despite the variability of the datasets.

Conclusion: Visual assessments showed the effectiveness of the program. The program computes ESV, EDV, stroke volume, strain and several other clinical parameters. The use of this program demonstrates that the semi-automated method can be used by physicians for the assessment of the heart using MRI image sequences with improved efficiency. In the future, we will be adding more features, and develop algorithms to perform the analysis in 3D space by combining the information from different views such as short and long axis sequences.
DEVELOPMENT OF AN IMMERSIVE ENVIRONMENT FOR SURGICAL PRE-OPERATIVE IMAGE VISUALIZATION

Andrew Whittle, Michelle Noga, Kumaradevan Punithakumar

**Background:** Virtual reality is an emerging field of technology which has not been fully explored in medicine. Applying this technology to medical imaging has the potential to augment traditional practices. The objective of this project is to develop a program to render temporal 3D datasets with the stereoscopic effect using zSpace (zSpace Inc., Sunnyvale, CA, USA) virtual reality technology for preoperative surgical planning.

**Methods:** Using the C++ programming language, we constructed a specialized rendering engine. This allowed us to develop a program that renders temporal DICOM images in 3D with stereoscopy. We focussed on rendering images with high fidelity and high resolution with low rendering latency. We developed specialized shader programs to handle colouring and cropping of the image. In addition to stereoscopy, a chromadepth effect was added to enhance depth recognition.

**Results:** We developed tools to allow the user to control the size and rotation of the image. The temporal playback feature allows the user to step through frames and play through them at various speeds. Colour transfer functions allow the user to enhance underlying anatomical details. We also implemented cropping functions to allow the user to see inside details.

**Conclusion:** Visual assessments using 3D echocardiography image sequences showed the effectiveness of the proposed technology against existing software. The program has features that allow the user to load a DICOM image, view, zoom, rotate, play, pause, and crop. Future studies will quantitatively assess the effectiveness of stereoscopic 3D rendering for analysing medical images against non-stereoscopic methods.
Quantification of Left Atrial Volumes in Cancer Patients Using a Novel Fully Automated 3D Echo Software Program

Tyler Lamb, Jonathan Choy, Marina Choy, Harald Becher

Background: Left atrial volume index (LAVi) is an echocardiographic parameter that has important prognostic and functional significance in cardiac disease. Three-dimensional echocardiography (3DE) is known to be more accurate than 2-dimensional echocardiography (2DE) at determining left atrial volumes. A fully automated software program has recently become available that quantifies the LAVi without the need for manual corrections. This software has the potential to decrease reporting times and increase laboratory efficiency. We therefore conducted a study to determine whether this novel, fully automated 3D echocardiography (A3DE) software tool produces similar LAVi measurements as those derived from standard 2DE.

Methods: Seventy-one consecutive cancer patients with acceptable acoustic windows were evaluated using both 2DE and A3DE. A commercially available scanner was used to acquire 3DE and 2DE recordings. LAVi was determined from the 2DE datasets using the biplane method of disks. A3DE analysis was performed using the novel fully automated software program, which determines the maximal LA long axis (which has different orientation than the LV long axis) and performs a volumetric measurement of the LA volume (Heart Model, Philips). The interobserver variability was measured on different datasets recorded during the same visit.

Results: LAVi measurements were obtained from data from all 71 subjects. The LAVi measurements were greater when using the A3DE method than with the 2DE biplane method of disks [29.6+7.3 ml (mean+SD) vs. 23.2+7.4 ml, p<0.05]. The LAVi as determined by each method for individual patients is displayed in figure 1. When using the American Society of Echocardiography guideline-recommended threshold for normal 2DE-derived LAVi, the LAVi by A3DE was classified differently (normal vs abnormal) in 15/71 patients (21%). Interobserver variability was assessed using the ‘% difference’, which equals the difference in measurements between observers divided by the average of the observers’ measurements. The % difference between 2 observers was 5.8 + 3.4% (mean + SD) for LAVi measurements by A3DE and 12.1 + 9.1% (mean + SD) for measurements using the 2D method.

Conclusion: The fully automated 3D echocardiographic method tested in this study is feasible in patients with adequate acoustic windows and reduces the interobserver variability. Compared to 2DE, LAVi’s derived from 3DE are larger, and different threshold values for normal LAVi need to be defined and applied.
QUANTIFICATION OF LEFT VENTRICULAR VOLUMES AND EJECTION FRACTION IN CANCER PATIENTS USING A NOVEL FULLY AUTOMATED 3D SOFTWARE PROGRAM: EXPLORING AN ALTERNATIVE TO 2D CONTRAST ECHOCARDIOGRAPHY

Tyler Lamb, Marina Choy, Ian Paterson, Jonathan Choy, Harald Becher

**Background:** Measurement of left ventricular ejection fraction (LVEF) by 2D contrast echocardiography (2DCE) is frequently used to monitor oncology patients for cardiotoxic effects of chemotherapy. With the goal of improving laboratory efficiency, we tested a novel automated 3D echocardiography (A3DE) software tool that automatically determines left ventricular volumes and LVEF without the need for manual corrections. We compared results using three different A3DE software settings to those obtained by 2DCE, which is the established method used to quantitatively assess LVEF and volumes in oncology patients at this institution.

**Methods:** Seventy-one consecutive cancer patients with acceptable acoustic windows were evaluated using both 2DCE and A3DE. A commercially available scanner was used to acquire 3D non-contrast and 2DCE recordings. Left ventricular end-diastolic volume index (LVEDVi), left ventricular end-systolic volume index (LVESVi) and LVEF were obtained using Simpson’s biplane method from 2DCE data. A3DE analysis was performed on each non-contrast 3D dataset using three different software presets, each of which has a different threshold for automatic detection of endocardial borders in end-diastole and end-systole.

**Results:** Data from seventy-one patients were obtained to produce a LVEDVi, LVESVi and LVEF using 2DCE and A3DE at each of the three different software settings. The A3DE recordings of ten patients were excluded from the LVEF difference analysis due to major discrepancies between the automatically determined left ventricular shapes and the endocardial borders. In the remaining sixty-one patients the mean LVEF was not significantly different between 2DCE and A3DE using setting 2 or setting 3. In thirty-nine of both the setting 2 and the setting 3 patients (64%), the difference in LVEF was less than 5% compared to that obtained with 2DCE (table 1).

**Conclusion:** In a population of patients with adequate image quality there is a large group in whom a fully automated non contrast 3D method provides very similar results to 2DCE. Therefore, for patients with good initial agreement between 2DCE and A3DE, it may be reasonable to undergo further monitoring of LVEF exclusively using A3DE.
Quantification of Epicardial Adipose Tissue in Non-Contrast and Contrast Computed Tomography Imaging: Comparison of Hounsfield Threshold

Lingyu Xu, Yuancheng Xu, Ian Paterson, Craig Butler

Background: Epicardial adipose tissue (EAT) volume is an important risk factor for cardiovascular disease, but its derivation from contrast enhanced CT scans is not well established. This study looks at systematic differences between EAT volume estimates from gated non-contrast cardiac CT (NC) datasets and gated contrast enhanced cardiac CT (CE) datasets.

Methods: We identified 15 subjects (age 70 ± 7.5 years, 12 males) with gated noncontrast and concurrently acquired contrast enhanced cardiac CT for a total of 30 datasets. EAT volumes were analyzed by a semi-automated 3D Fat analysis (Tera-recon). EAT was defined by radiodensity using hounsfield threshold (-190U, -30U) on NC datasets and formed the gold standard of EAT estimation. Previously reported thresholds of: (-190U, -30U), (-190U, -15U), (-175U, -15U) were used for CE datasets. We also derived custom thresholds for each NC:CE comparison by comparing the differences (Diff) of EAT radiodensity between NC and CE datasets at standardized regions of interest (ROI) (Figure 1). We then used the median parameters of the custom thresholds to re-analyzed EAT from CE datasets.

Results: The EAT volume in NC and CE datasets using different Hounsfield thresholds are showed in Table. 1. EAT derived from CE datasets consisted underestimated EAT volume derived by NC studies at standard thresholds (-190U,-30U; ∆= 37.4 ± 9.8 cm³ (17.4%)) as well as (-190U,-15U) and (-175U,-15U). The Diff was -26.7 ± 5.8 U. We set the lower limit threshold as -185U and the individually adjusted upper limit as (-30+Diff-5)U ranging from -20 U to -5U with a median of -7U. The EAT volume on CE images with threshold from -185U to (-30+Diff-5)U was close to NC EAT volume (∆=3.2%, P= 0.0003), despite that it was still significantly smaller. The CE EAT volume with threshold (-185U, -7U) was the closet to NC EAT volume (211.7 ± 54.0 vs. 215.5 ± 51.8 cm³, P >.05, ∆=1.8%). NC EAT volume with threshold (-190,-30U) was highly correlated (r = 0.99) with, and had high agreement (P= 0.250 by Bland-Altman Analysis) with CE EAT volume with threshold (-185U, -7U).

Conclusion: EAT volumes estimated from contrast enhanced cardiac CT underestimate EAT volumes derived from noncontrast studies. Altering the Hounsfield units for EAT assessment on contrast enhanced CT scans to -185U to -7U provided the best agreement with standard estimates of EAT volume from non-contrast CT scans. Our Hounsfield threshold holds true for our derivation cohort, but requires validation in a separate series of datasets.
Figure 1. Epicardial adipose tissue radiodensity was derived from para-coronary regions of interest (red circles) at the same axial slice level: A) the Left Panel: contrast enhanced CT datasets; B) the Right Panel: non-contrast coronary artery calcium score datasets.

Table 1. Comparison of EAT volume in NC and CE CT data with different thresholds

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<tbody>
<tr>
<td>EAT Volume (cm³)</td>
<td>215.5 ± 51.8</td>
<td>178.1 ± 50.2</td>
<td>200.0 ± 53.0</td>
<td>199.3 ± 53.0</td>
<td>208.7 ± 53.2</td>
<td>211.7 ± 54.0</td>
</tr>
<tr>
<td>P (compared to non-contrast EAT)</td>
<td>1.00</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>0.0003*</td>
<td>0.0526</td>
</tr>
</tbody>
</table>

Values given as mean ± standard deviation unless otherwise indicated. * means P-value < .05.
Abbreviations: EAT: epicardial adipose tissue; NC: non-contrast; CE: contrast enhanced; CT: computed tomography.
REGIONAL EPICARDIAL ADIPOSE TISSUE RADIODENSITY IS INDEPENDENTLY ASSOCIATED WITH CORONARY ARTERY LESIONS

Lingyu Xu, Yuancheng Xu, Ian Paterson, Craig Butler

**Background:** Epicardial adipose tissue (EAT) radiodensity evaluated by computed tomography (CT) is increasingly associated with coronary lesions and adverse coronary outcome. EAT may exert paracrine effects on the coronary artery disease themselves to promote atherosclerosis. We hypothesized that para-coronary regional EAT radiodensity will have better correlation to coronary artery disease than mean slice specific EAT radiodensity.

**Methods:** We measured EAT volume in 40 patients (age 40 ± 8 years, 33 males) using a hounsfield threshold of -190U to -30U on non-contrast coronary artery calcium score datasets. EAT analysis was performed on a semi-automated 3D Fat analysis software (Tera-recon). We selected an axial slice that included the proximal segments of all three major coronary arteries. A general EAT radiodensity (RD_General) of this slice is automatically generated based on the total EAT area. We evaluated regional radiodensity (RD_Regional) in selected standardized regions of interest (ROI) with an area of 30mm² within EAT closest to LAD (2 to 3 ROIs), RCA (3 to 5 ROIs) and LCX (1 to 2 ROIs) (Figure 1). Average EAT radiodensity of ROIs was calculated. Severe CAD stenosis is defined as coronary stenosis exceeding 70%. Severe coronary calcification was defined as a coronary artery calcium (CAC) Agatston score > 400.

**Results:** RD_General was 82.8 ± 5.9 HU, whilst RD_Regional was 95.2 ± 7.6 HU. Compared to patients with non-severe coronary stenosis, patients with severe coronary stenosis had significant higher RD_Regional (-92.4 ± 7.5 vs. -97.7 ± 6.9 HU, P = 0.0253), but only slightly higher RD_General (-82.4 ± 6.4 vs. -83.1 ± 5.6 HU, P = 0.6804). Compared to patients with non-severe coronary calcification, patients with severe coronary calcification had significant higher RD_Regional (-92.9 ± 7.7 vs. -99.5 ± 5.3 HU, P = 0.0066), but only slightly higher RD_General (-82.4 ± 6.0 vs. -83.5 ± 5.8 HU, P = 0.5745). Only RD_Regional was independently associated with severe coronary stenosis (odds ratio (OR) 1.11 for 1 HU increase, P = 0.035) and with severe coronary calcification (OR 1.16 for 1 HU increase, P = 0.014). An optimal cutoff value of RD_Regional by Receiver Operating Characteristic analysis was computed as -96.5 HU. For patients with RD_Regional > -96.5 HU had much higher incidence of severe coronary stenosis (OR 4.55, P = 0.028) and severe coronary calcification (OR 5.6, P = 0.018).

**Conclusion:** Non-contrast para-coronary Regional EAT radiodensity had better correlation with coronary artery disease compared to general EAT radiodensity.
Figure 1: Epicardial adipose tissue radiodensity was assessed from para-coronary regions (figure 1A RD_ROI) of interest or from the mean value of total slice specific EAT radiodensity (figure 1B RD_General) at the same axial slice level.
BRAIN CORRELATES OF MENTAL STRESS-INDUCED MYOCARDIAL ISCHEMIA

Douglas Bremner, Carolina Campanella, Zehra Khan, Majid Shah, Muhammad Hammadah, Kobina Wilmot, Ibhar Al Mheid, M.D., 2Ernest V. Garcia, Jonathon Nye, Laura Ward, Brad Pearce, Amit Shah, Arshed Quyyumi, Viola Vaccarino, Paolo Raggi

Background: Coronary artery disease (CAD) disease is a major cause of morbidity and mortality, but risk factors and mechanisms predisposing to its development remain unclear. This has led to increased attention to the role of behavioral factors like emotional stress. Brain areas involved in memory and the stress response, including medial prefrontal cortex, insula and parietal cortex, also have outputs to the peripheral cardiovascular system. The purpose of this study was to assess the effects of mental stress on brain and cardiac function in patients with CAD. A secondary goal was to assess whether symptoms of depression interact with mental stress on these outcomes.

Methods: CAD patients (N=170) underwent imaging of the brain with [O-15] water positron emission tomography (PET) and imaging of the heart with [Tc-99m] sestamibi single photon emission tomography (SPECT) during mental stress (arithmetic and public speaking) and under control conditions.

Results: Patients with mental stress-induced myocardial ischemia (MSI) showed increased activation with stress in anterior cingulate, inferior frontal gyrus, and parietal cortex. This was seen with both arithmetic stress and public speaking stress. Arithmetic stress was additionally associated with insula activation, and public speaking with precentral gyrus and middle temporal gyrus activation. Patients with symptoms of depression had increased anterior cingulate activation with stress.

Conclusion: These findings suggest that mental stress-induced myocardial ischemia is associated with activation in brain areas involved in the stress response and autonomic regulation of the cardiovascular system. Altered brain reactivity to stress could possibly represent a mechanism through which stress leads to increased risk of CAD-related morbidity and mortality.
ANGINA AND MENTAL STRESS INDUCED CARDIOVASCULAR ISCHEMIA: SEX DIFFERENCES

Pratik Pimple, Muhammad Hammadah, Kobina Wilmot, Ronnie Ramadan, Ibhar Al Mheid, Lisa Elon, Oleksiy Levantsevych, Samaah Sullivan, Ernest V. Garcia, Jonathon Nye, Amit J. Shah, MD, MSCR; 1,2 Laura Ward, Puja Mehta, J. Douglas Bremner, Arshed A. Quyyumi, Viola Vaccarino, Paolo Raggi

Background: Mental stress-induced myocardial ischemia (MSIMI) is a frequent phenomenon in patients with coronary artery disease (CAD). Women with CAD tend to have more MSIMI and more angina symptoms than men, but whether the association between MSIMI and angina burden differs in women and men, is unknown. Our objective is to investigate the association between angina and MSIMI in individuals with CAD, and assess effect modification by sex. We also compared these results with those obtained with a conventional stress test.

Methods: Design - Cross-sectional study Participants: 907 individuals with stable CAD. Exposure: Angina frequency during daily life in the previous 4 weeks, assessed with the Seattle Angina Questionnaire’s angina-frequency subscale. MSIMI assessed with myocardial perfusion imaging in conjunction with mental stress (standardized public speaking task). A conventional stress test was used as a control condition. Ischemia was assessed as a continuous variable (percent of ischemic myocardium) and as a categorical variable.

Results: The mean age was 60 years, 34% were women, and 41% African-Americans. Overall, 338 individuals (37%) reported angina over the previous 4 weeks. After adjusting for demographic and clinical risk factors, women with angina had over twofold more ischemic myocardium with mental stress compared to women without angina (1.8% vs. 0.8%), while there was no such difference in men (1.2% vs. 1.0%), p=0.04 for interaction. No association was found between angina and conventional stress-induced ischemia for either women or men. Results were similar for ischemia as a categorical variable.

Conclusion: In women, but not in men, angina symptoms may be a marker of vulnerability towards ischemia induced by psychological stress. These results highlight the neurocardiac origins of anginal symptoms in women, and may have important implications for the management and prognosis of women with angina.
SEX DIFFERENCES IN HEMODYNAMIC AND MICROVASCULAR MECHANISMS OF MYOCARDIAL ISCHEMIA INDUCED BY MENTAL STRESS


Background: To investigate sex-specific vascular mechanisms for mental stress-induced myocardial ischemia (MSIMI).

Methods & Results: 678 patients with coronary artery disease underwent myocardial perfusion imaging before and during a public speaking stressor. The rate-pressure product (RPP response) was calculated as the difference between the maximum value during the speech minus the minimum value during rest. Peripheral vasoconstriction by peripheral arterial tonometry (PAT) was calculated as the ratio of pulse wave amplitude during the speech over the resting baseline; ratios < 1 indicate a vasoconstrictive response. MSIMI was defined as percent of left ventricle (LV) that was ischemic and as a dichotomous variable. Men (but not women) with MSIMI had a higher RPP response than those without MSIMI (6,500 vs. 4,800 mmHg bpm), while women (but not men) with MSIMI had a significantly lower PAT ratio than those without MSIMI (0.5 vs. 0.8). In adjusted multivariable linear regression analyses, each 1,000-unit increase in RPP response was associated with 0.31% (95% CI: 0.21, 0.40) increase in inducible ischemia among men, while each 0.10-unit decrease in PAT ratio was associated with 0.23% (95% CI: 0.11, 0.35) increase in inducible myocardial ischemia among women. Results were independent of conventional stress induced myocardial ischemia.

Conclusion: Women and men have distinct cardiovascular reactivity mechanisms for MSIMI. For women, stress-induced peripheral vasoconstriction with mental stress, and not increased hemodynamic workload, is associated with MSIMI, while for men it is the opposite. Future studies should examine the impact of these findings on long-term outcomes.
INFLAMMATORY RESPONSE TO MENTAL STRESS AND MENTAL STRESS INDUCED MYOCARDIAL ISCHEMIA


Background: Mental stress-induced myocardial ischemia (MSIMI) is associated with increased risk of adverse cardiovascular outcomes, yet the underlying mechanisms are not well understood. We measured the inflammatory response to acute laboratory mental stress in patients with coronary artery disease (CAD) and its association with MSIMI with the hypothesis that patients with MSIMI will have a higher inflammatory response to mental stress in comparison to those without ischemia.

Methods: Patients with stable CAD underwent 99mTc sestamibi myocardial perfusion imaging during mental stress testing using a public speaking stressor. MSIMI was defined as impaired myocardial perfusion using a 17-segment model. Inflammatory markers including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), matrix metallopeptidase 9 (MMP-9) and high-sensitivity C reactive protein (hsCRP) were measured at rest and 90 minutes after mental stress.

Results: Of 556 patients, (mean age 63±9 years, 75% male), 81 (14.5%) developed MSIMI. Mental stress resulted in a significant increase in IL-6, MCP-1, and MMP-9 (all p<0.001), but not hs-CRP. However, the changes in these markers were similar in those with and without MSIMI. Neither resting levels of these biomarkers, nor their changes with mental stress were associated with MSIMI.

Conclusion: Mental stress is associated with acute increases in several inflammatory markers. However, neither the baseline inflammatory status nor the magnitude of the inflammatory response to mental stress over 90 minutes were associated with MSIMI.
A POPULATION-BASED STUDY OF ADHERENCE TO APPROPRIATE USE CRITERIA AND GUIDELINE RECOMMENDATIONS FOR IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Rochelle Bernier, Evan Lockwood, Sajad Gulamhusein, Randall Williams, Lucas Valtuille, Soori Sivakumaran, Tomasz Hruczkowski, Shane Kimber, Roopinder K Sandhu

Background: Guidelines exist to help physicians identify patients who would benefit from implantable cardioverter defibrillator (ICD) therapy however limited data exists regarding physician adherence to guideline recommendations. Therefore, the aims of this study were to determine the proportion of patients receiving ICD therapy according appropriate use criteria and guideline recommendations and to identify reasons for non-adherence to appropriate use criteria.

Methods: We performed a retrospective review of all ICDs implanted from January 1, 2015-December 31, 2016 in Edmonton, Alberta. Patients were evaluated by an electrophysiologist and a consensus decision to implant was made during a formal peer review process. We classified implants according to the 2013 Appropriate Use Criteria for ICDs and CRT, 2008 ACC/AHA/HRS ICD guidelines, 2012 ACCF/AHA HRS Focused Update and the 2013 CCS CRT guidelines.

Results: A total of 897 devices were implanted (22 implants were excluded due to missing information, n=875). Baseline characteristics are shown in Table I. The mean age was 63 ±13; 82% were male; mean ejection fraction of 0.31 ±0.13 and 62% of implants were for primary prevention. Of the procedures performed, 64% were new implants, 29% were generator changes, and 10% were upgrades. The majority of ICD implants met ‘appropriate’ (91%) and class I indications (70%) while no procedures had a class III indications (Figure 1). Non-adherence to appropriate use criteria was demonstrated in 14% (n=48) of implants. Reasons for non-adherence included no existing appropriate use criteria (n=32, 67%), recent revascularization (n=8, 17%), research participation (n=4, 8%) and recent myocardial infarction (n=4, 8%).

Conclusion: In this population-based study, we found that our formal process of specialist evaluation and peer-reviewed consensus was highly effective at achieving consistency with appropriate use criteria and guideline-derived recommendations.

Figure 1 ICD implants classified according to appropriate use criteria, guideline recommendations and CCS CRT guidelines.
QIQC-CLIN-2

UTILIZATION OF AN ACUTE RESPONSE ALGORITHM ON THE INPATIENT CARDIOLOGY SERVICE AT THE MAZANKOWSKI ALBERTA HEART INSTITUTE: A PILOT STUDY

Lisa Marco, Skylar Pehlke, Dr. Debraj Das, Dr. Evan Martow, James Simon, Stacy Krenkel, Dr. Wayne Tymchak, Miriam Shanks

Background: In 2015, a multidisciplinary team at the Mazankowski Alberta Heart Institute identified a gap in response times to deteriorating patients on the cardiology unit during evenings and weekends. Through a quality assurance review in response to a patient incident, a collective uncertainty surrounding response times and expectations was identified. An Acute Response Algorithm (ARA) was created to improve communication, standardize nursing response and provide a structured approach in the management of unstable patients. The aim was to improve timely access to physician assessment and enhance quality patient care. After implementation, an evaluation process was developed and applied to determine the clinical efficacy and utility of the ARA.

Methods: Utilizing the Plan-Do-Study-Act methodology, the quality initiative involved two phases. The first (initiated November 2015) focused on creation and implementation of the ARA (Figure 1). The ARA was developed in collaboration with management, cardiologists, senior residents, and frontline nurses. The ARA is a standardization of activation triggers, response times, and expectations. The second phase (initiated January 2017) addressed adherence to the ARA protocol. A process was created to capture nursing concerns resulting in pages to residents, and flag clinical situations. The team was able to identify when ARA trigger criteria were met but ARA was not activated over a four week period. Through cross-referencing and chart reviews, these tracking sheets helped determine appropriateness of the ARA activation and identify potential concerns.

Results: There were 73 on-call concerns that were recorded in the assessment period. Calls were most frequently related to medication orders (41%, N=29/73), rhythm disturbances (28%, N=20/73) and chest pain (13%, N=9/73). The ARA was activated in 14% (N=10/73) of calls. Appropriate activation occurred in 90% (N=9/10) of circumstances. The ARA was inappropriately not activated in 5% of cases (N=4/73); two were related to clinically significant deviations in blood pressure and the remaining two were related to refractory chest pain.

Conclusion: The development of the ARA has helped bridge gaps in care identified by a multidisciplinary team on an inpatient cardiology service at the Mazankowski Alberta Heart Institute. Through collaboration, an improved understanding of the ARA and openness for learning opportunities were developed, resulting in improved communication, standardized nursing care, provision of timely treatment, and mitigation of adverse patient outcomes. When the ARA was inappropriately not activated cases were identified as targets for educational intervention. Implementations of clinical care standards enhanced patient care and provided a framework for quality initiatives.
Cardiology SAS/SA6 Response Pathway

Goals of the Acute Response Algorithm:
- Junior (Jr.) Resident will assess the patient within 15 minutes of being notified of the urgent concern and determine appropriate treatment.
- Senior (Sr.) Resident is to be informed early and triage the situation appropriately and review all urgent concern cases with the Jr. Resident.

**Patient issue/concern**

**URGENT concerns: Acute Response Algorithm**

- Chest pain unrelieved with 3 sprays of nitroglycerin 5 min apart
- Acute worsening shortness of breath/Rapidly increasing oxygen requirements
- Signs & Symptoms of a stroke/slurred speech, sudden numbness/weakness/paralysis in the face/ arm or leg, sudden severe headache +/- vomiting, dizziness, altered LOC, trouble walking (severe dizziness, loss of balance/coordination), sudden changes in vision (blurred/double vision/loss of vision in one or both eyes)
- Decrease/Change in LOC with GCS greater than 3
- Clinical signs of bleeding (i.e.: hemoptysis, melena, hematemesis) in an otherwise stable pt
- New cardiac rhythm/New ECG changes/12 lead ECG performed STAT
- Asymptomatic sustained VT greater than 30 seconds
- Symptomatic bradycardia less than 50 bpm
- Hypotension (SBP less than 90 mmHg, or a drop in SBP by more than 40 mmHg) associated with symptoms
- Asymptomatic hypertension greater than 200 SBP or greater than 110 DBP
- Nursing staff concerned about the physiological condition of the patient

On Call Response Team Members:
- Charge Nurse
- Bedside Nurse
- Senior Cardiology Resident
- Junior Cardiology Resident

Documentation:
- If the Junior Resident does not respond to 2 consecutive pages 5 minutes apart + 1 overhead call, the Senior Resident will be notified.
- If the Junior Resident does not arrive to the ward within 15 minutes of receiving the page, the Senior Cardiology Resident will be notified.
- If the Senior Cardiology Resident does not respond to 2 consecutive pages 5 minutes apart + 1 overhead call, the Attending Cardiologist on call for COU will be swapped.

Resident Documentation:
All direct encounters with patient or family should be recorded in the progress notes. Once the Jr. Resident reviews the concern/situation with the Sr. Resident, the resident (Sr. or Jr.) needs to document that the concern was reviewed by the Sr. Resident in the progress notes.

Nursing Documentation:
All phone/person conversations with the Sr. or Jr. Resident needs to be charted in the nurses’ notes. As per CARNA’s documentation guidelines include the following in your nurse’s notes:
- Physician name and designation
- Time of conversation
- The concerns discussed and the plan of care

**IF FASTER RESPONSE IS REQUIRED (I.E. CARDIAC ARREST, RESPIRATORY ARREST, ACUTE HEMODYNAMIC CHANGES ETC.) A CODE BLUE SHOULD BE CALLED AS PER HOSPITAL POLICY!**
V ASD-CLIN-1

GENDER DISPARITIES IN HOSPITALIZATION AND MORTALITY RATES FOR VENOUS THROMBOEMBOLISM

Sola Mansour, Ghazi Alotaibi, Cynthia Wu, Michael Sean McMurtry

Background: Venous thromboembolism (VTE) is a major health problem for both men and women. Whether gender disparities exist for outcomes after acute VTE is unknown. We sought to measure gender-specific rates of hospitalization for and mortality from acute VTE.

Methods: We used a population-based administrative dataset from Alberta, Canada, covering the years 2002 to 2012. We used Poisson regression to measure the incidence rate ratio for hospitalization and Cox regression to test for gender disparities in short-term all-cause mortality after adjusting for potential confounders.

Results: Of those diagnosed with VTE, 55.9% were women. The proportion of hospitalized women for VTE was 24.4%, versus 27.8% in men (p<0.001). The risk adjusted incidence rate ratio for VTE hospitalization increased with age for both genders. While women younger than 80 years old were less likely to be hospitalized than men, gender disparities for the risk of hospitalization were not significant after age 80 (p=0.93). The adjusted 90-day all-cause mortality rate for women was 4.0% compared to 4.9% in men (adjusted HR=1.0, p=0.49).

Conclusion: Women with acute VTE were less likely than men to be hospitalized in most age groups, but gender disparities in short-term all-cause mortality were not found.
AWARDS
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:

2016 - Dora Gyenes
2015 - Dr. Suman Dhesi
2014 - Dr. Dierdre O’Neill
2013 - Dr. Vikram 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. 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:

2016 - Joseph Martin Penninger, MD, Institute for Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria
2015 - Dr. Zahi A. Fayad, Mount Sinai Hospital, New York, NY
2013 - Dr. Francis G. Spinale, University of South Carolina, Columbia, SC
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 Fremes, 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
Dr. Richard E. Rossall Award

Dr. Richard Rossall was a founder of the Division of Cardiology at the University of Alberta. During his leadership as Divisional Director for 20 years, Dr. Rossall was successful in building a state of the art Cardiology program. He is best known for his organizational, teaching and clinical skills. Colleagues have described him as a master diagnostician with superb clinical acumen. One of his major innovations included the development of a computer based teaching module for trainees which was well ahead of its time. The first ever Postgraduate Training Program at the University of Alberta was created and led by Dr. Rossall. His talents were recognized nationally with successful tenure as the President of the Canadian Cardiovascular Society and an awardee of the Governor General’s Confederation Medal.

The Richard E. Rossall Arrhythmia and Valvular Heart Disease Trust Fund was created with a generous donation from the Dr Rossall’s spouse, Mrs. Joan Rossall. The interests generated from the management of the fund will be distributed annually to support a research project submitted by a Cardiology Resident to a scientific review committee.

PAST RECIPIENTS:

2016 - Vikram Gurtu
2015 - Vikram Gurtu
Dr. Francis X. Witkowsi 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:

2016 - Subhash Das
2015 - Dr. Roxane Paulin
2014 - Dr. Valibhav B. Patel
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
2006 - Dr. Clifford Folmes
2005 - Dr. Hernando Leon
2004 - Dr. Istvan Baczko
2003 - Dr. Sean McMurtry
2002 - Dr. Zlatko Pozeg
2001 - Dr. Lei Guo
2000 - Dr. Po-Yin Cheung
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