20TH ANNUAL

MAZANKOWSKI
CARDIAC SCIENCES RESEARCH DAY

UNIVERSITY OF ALBERTA
JUNE 10, 2016
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CARDIAC SCIENCES RESEARCH DAY ORGANIZING COMMITTEE

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Dr. Richard Lehner, Co-Chair
Deanna Tretiak
Alison Müller
Anmol Shahid
Kelly Davies - Animatters Inc.

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Dr. Jason Dyck Dr. Evangelos Michelakis
Dr. Michelle Graham Dr. Frances Plane
Dr. Richard Lehner Dr. Roopinder Sandhu
June 10, 2016

Dear Colleagues,

Welcome to the 20th Annual Cardiac Sciences Research Day. It is always a pleasure and a honour to preside over this day of showcasing of the best cardiovascular science developed in our institution. Both the basic and clinical sciences are well represented and numerous interesting abstracts have been submitted. This is living proof of the productivity and vitality of our cardiovascular environment.

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

- Dr. Peter Libby, MD, Cardiovascular Medicine Brigham and Women’s Hospital, Mallinckrodt Professor of Medicine, Harvard Medical School, Boston, MA, USA.
  Dr. Libby will be presenting: *Novel Mechanisms of Acute Coronary Syndromes*

- Dr. Josef Martin Penninger, MD, Scientific Director, Institute for Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria.
  Dr. Penninger will be presenting: *Cardiac Regeneration*

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

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

Warm regards,
Paolo Raggi, MD, FACC, FACP, FASNC
Chair, CSRD Organizing Committee
# 20TH ANNUAL MAZANKOWSKI CARDIAC SCIENCES RESEARCH DAY

**0745 – 1730 | FRIDAY, JUNE 10, 2016**

**ALLARD FAMILY LECTURE THEATRE, ROOM 1080**

**KATZ GROUP CENTRE FOR PHARMACY AND HEALTH RESEARCH**

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Hyperoxia Reduces Oxygen Consumption in Children
with Pulmonary Hypertension

1100 Gareth Armanious, Jessica Gifford, Catharine Trieber, Howard Young
Genetic Landscape of the Calcium Regulatory Protein Phospholamban in Dilated Cardiomyopathy
- Functional Underpinnings of Hereditary Dcm

1115 Dora Gyenes, Joseph Atallah, Charlene Robertson, Gwen Alton, Irina Dinu, Fahimeh Moradi, Winnie Savard, Lisa Hornberger
Altered Umbilical Arterial Blood Flow in the 3rd Trimester and its Association with Clinical and Neurodevelopmental Outcomes in Children with Hypoplastic Left Heart Syndrome

1130 - 1250 Lunch / Poster Viewing

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

1300 - 1400 Speaker – Josef Martin Penninger, MD
Scientific Director, Institute for Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria
Topic: Cardiac Regeneration

1415 - 1515 Podium Abstract Session
Chairs – Dr. Jason Dyck & Dr. Michelle Graham

1415 Valentina Back, Frances Plane, Paul Jurasz
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1430 Pishoy Gouda, Debraj Das, Alex Clark, Justin Ezekowitz
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1445 Sotirious Zervopoulos, Aristeides E. Boukouris, Alois Haromy, Adam Kinnaird, Vikram Gurru, Trevor Stenson, Evangelos D. Michelakis
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1515 - 1530 Coffee Break / Poster Viewing

1530 - 1630 Podium Abstract Session

Chairs – Dr. Frances Plane & Dr. Roopinder Sandhu

1530 Pavel Zhabeyev, Brent McLean, Bart Vanhaesebroeck, Gavin Y. Oudit

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1545 Jiali Luan, Richard Thompson, Ian Paterson, Kumaradevan Punithakumar, Michelle Noga

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1600 Bruno Saleme, Adam Kinnaird, Aristeidis Boukouris, Sotirios Zervopolous, Vikram Gurtu, Gopinath Sutendra

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1615 Marc Benoit, Sean M Bagshaw, Colleen M Norris, Mohamad Zibdawi, W.D. Chin, David B Ross, Sean van Diepen

Association Between 24/7 Intensivist-Only Management and Post-Operative Complications, Resource Utilization and Outcomes Among Cardiac Surgery Patients: a Propensity Matched Cohort Study

1630 - 1700 Abstract Judging, Awards Ceremony & Closing Remarks

1700 Reception
GUEST SPEAKER BIOGRAPHIES
Peter Libby, MD

Peter Libby, MD, is a cardiovascular specialist at Brigham and Women’s Hospital in Boston, Massachusetts, and holds the Mallinckrodt Professorship of Medicine at Harvard Medical School. He served as Chief of Cardiovascular Medicine at BWH from 1998 - 2014. His areas of clinical expertise include general and preventive cardiology. His current major research focus is the role of inflammation in vascular diseases such as atherosclerosis. Dr. Libby has received numerous awards and recognitions for his research accomplishments, including the Gold Medal of the European Society of Cardiology (2011), the Basic Research Prize of the American Heart Association (2011), the Anitschkow Prize in Atherosclerosis Research of the European Atherosclerosis Society (2013), and the Distinguished Achievement Award of the Heart Failure Association of the European Society of Cardiology (2014).

Dr. Libby’s professional memberships include the Association of American Physicians, the American Society for Clinical Investigation, and elected honorary memberships in the British Atherosclerosis Society, the Japan Circulation Society, and the Japanese College of Cardiology. He has served as the President of the Association of University Cardiologists. He also has served in many roles as a volunteer for the American Heart Association, including chairman of several research committees and member of the executive committees of the Councils on Arteriosclerosis, Circulation, and Basic Science. He presided the American College of Cardiology’s Research Allocations Peer Review Committee for two terms. He has frequently consulted for the National Heart, Lung, and Blood Institute, including a 5-year term on the Board of Scientific Councilors. He directed the DW Reynolds Cardiovascular Clinical Research Center and two cycles of Leducq Foundation Awards, and has received continuous funding from the NHLBI for several decades.

...cont’d on next page
An author and lecturer on cardiovascular medicine and atherosclerosis, Dr. Libby has published extensively in medical journals including Circulation, Journal of Clinical Investigation, Proceedings of the National Academy of Sciences, New England Journal of Medicine, and Nature. He is an Editor of Braunwald’s Heart Disease. Dr. Libby also contributed chapters on the pathogenesis, treatment, and prevention of atherosclerosis to many editions of Harrison’s Principles of Internal Medicine. He has held numerous visiting professorships and delivered more than 80 major named or keynote lectures throughout the world.

Dr. Libby earned his medical degree at the University of California, San Diego, and completed his training in internal medicine and cardiology at the Peter Bent Brigham Hospital (now Brigham and Women’s Hospital). He also holds an honorary MA degree from Harvard University, and an honorary doctorate from the University of Lille, France
JOSEF MARTIN PENNINGER, MD

Josef Penninger, MD was formerly a lead researcher at the Amgen Research Institute in Toronto. In 2002 he accepted the appointment as founding director of the newly established Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences in Vienna, Austria. Major achievements include pioneering insights into the molecular basis of osteoporosis and breast cancer, as well as the study of metastatic spread. His group has also developed the first haploid embryonic stem cells for functional genetics. Using these approaches, Josef Penninger tries to establish basic principles of development and disease pathogenesis. He has authored and co-authored more than 530 scientific papers, of which a large number was published in leading scientific journals such as “Nature” and “Science”. Josef Penninger’s major awards include the Descartes Prize, the Wittgenstein Prize of the Austrian Federal Government, the Ernst Jung Prize for medical excellence, the Award as Elected Fellow of the American Association for the Advancement of Science, the Innovator Award from Era of Hope/DOD and a second ERC Advanced grant.
ORAL ABSTRACTS
MILD THERAPEUTIC HYPOBARIA IMPROVES LEFT VENTRICULAR FUNCTION AFTER ACUTE MYOCARDIAL INFARCTION IN MICE

Anmol Shahid, Michael Sean McMurtry

**Background:** Humans living at higher elevations have lower risk for myocardial infarction (MI) and better post-MI survival. We have shown that acute reductions in atmospheric pressure enhance arterial vasodilation in an endothelium-independent manner ex vivo and reduce afterload in vivo in mice. We hypothesized that afterload reduction induced by mild therapeutic hypobaria after acute MI would improve myocardial function.

**Methods:** Left-anterior descending artery (LAD) ligation was performed on three-month old C57BL6 males. Group A mice (control, n=9) were allowed to recover from the surgery at atmospheric pressure (754 mmHg). Group B mice (n=8) were placed in a hypobaric chamber to recover from the LAD ligation for 3-hours at 714 mmHg, a pressure chosen to mimic an elevation of 1500 m and avoid hypoxemia. The successful induction of anterior MI was confirmed by echocardiography 24 hours after the surgery. Group B mice were administered 3-hours of hypobaric treatment daily for 7 days. Echocardiographic evaluation of left ventricular (LV) function was performed for all mice on Day 8.

**Results:** Echocardiography confirmed large anterior MI’s in both groups with no difference in ejection fraction (EF) or cardiac output at day 1. After 7 days of therapeutic hypobaria, there was a 14.2±5.3% improvement in EF for Group B mice (p<0.01 versus Day 1), and no change for Group A mice. Similarly, cardiac output and stroke volume increased by 11.48±3.9 µL/min and 24.33±8.3 µL, respectively, in Group B mice (p<0.01 versus Day 1) after 7 days of hypobaric treatment while Group A mice showed no significant improvement.

**Conclusion:** We conclude that acute afterload reduction achieved by mild therapeutic hypobaria improves myocardial function after acute MI in mice. This finding may have translational potential as a novel therapy for acute MI in humans.
LONG-TERM SURVIVAL IN CHRONIC KIDNEY DISEASE PATIENTS WITH STABLE ISCHEMIC HEART DISEASE: EVALUATING THE IMPACT OF CORONARY REVASCULARIZATION

Jay Shavadia, Matthew James, Danielle Southern, Robert C. Welsh, Kevin R. Bainey

**Background:** Contemporary clinical trials of revascularization versus medical management in stable ischemic heart disease (SIHD) have shown the benefits of optimal medical therapy (OMT) with no change in survival. However, chronic kidney disease (CKD) patients have been under-represented in these studies despite their heightened risk of cardiovascular (CV) death. Using a large contemporary angiographic registry, we examined the incidence, demographic profile and clinical outcome of coronary revascularization in addition to OMT compared to OMT only in patients with CKD presenting with SIHD.

**Methods:** We studied 17,910 SIHD patients with angiographic evidence of flow-limiting CAD (≥70% stenosis in at least one major epicardial vessel) using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) prospective registry in Alberta, Canada between January 1, 1999 to March 31, 2014. Comparisons were made between patients with dialysis-dependent CKD, non-dialysis CKD (estimated glomerular filtration rate [eGFR] <30ml/min, 30-45ml/min, 45-60ml/min), and no CKD (eGFR >60ml/min [reference group]). Long-term survival by treatment group (revascularization [coronary artery bypass grafting surgery or percutaneous coronary intervention] versus conservative management) was explored. A Cox proportional-hazards analysis was performed within each category of kidney function according to treatment received.

**Results:** Of our study cohort, 2490 patients (13.9%) had CKD. In general, these patients were older (except dialysis CKD), less commonly male and had higher rates of diabetes and prior heart failure compared to patients without CKD (Table). Overall, revascularization occurred less commonly in the CKD compared to the non-CKD patients; within the CKD population, the observed frequency of revascularization declined with worsening indices of renal function until dialysis-dependent (Table). At a median of 8.0 years (interquartile range 3.2 years), a consistent relationship was noted between the degree of CKD and long-term death (Figure). Within the spectrum of CKD patients, revascularization improved long-term survival, which appears most pronounced in dialysis patients (dialysis-dependent: 43.2% vs. 70.5%, adjusted hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.17-0.58; eGFR <30: 26.2% vs. 37.1%, adjusted HR 0.68, 95% CI 0.40-1.15; eGFR 30-45: 28.7% vs. 38.2%, adjusted HR 0.64, 95% CI 0.46-0.90; eGFR 45-60: 19.2% vs. 30.5%, adjusted HR 0.56, 95% CI 0.44-0.70) (Figure).

**Conclusion:** Results from this large angiographic registry of SIHD patients confirm findings of poor survival with progression of CKD. Additionally, lower rates of revascularization were observed, yet long-term survival favoring revascularization was demonstrated. Acknowledging the evolution of OMT and contemporary revascularization strategies in this understudied population, these hypothesis-generating results require validation within a randomized trial focusing on CKD patients.
Long-term mortality and treatment stratified by severity of CKD

- Diastolic: 70.3% Revascularization, 37.7% Conservative management
- CKD (eGFR<30): 37.3% Revascularization, 38.2% Conservative management
- CKD (eGFR 30-45): 28.2% Revascularization, 34.2% Conservative management
- CKD (eGFR 45-60): 19.2% Revascularization, 30.5% Conservative management
- No CKD: 12.4% Revascularization, 59.6% Conservative management

Median follow-up 8.0 (IQR 3.2) years
TISSUE INHIBITOR OF MATRIX METALLOPROTEINASE-3 (TIMP3) PROVIDES BENEFICIAL EFFECTS POST-MI BY PROMOTING ANGIOGENESIS

Abhijit Takawale, Pu Zhang, Wang Wang, Ratnadeep Basu, Xiuhua Wang, Allan Murray, Zamaneh Kassiri

Background: Myocardial infarction (MI) results in loss of cardiomyocytes, adverse extracellular matrix (ECM) remodelling, leading to left ventricular (LV) dilation and dysfunction. Tissue inhibitors of metalloproteinase (TIMPs) are MMP inhibitors, main regulators of ECM integrity. TIMPs can also regulate other aspects of myocardial remodeling such as hypertrophy, fibrosis and inflammation. TIMP3 levels are reduced in the peri-infarct zone within 24 hours post-MI in mice. We hypothesized that replenishment of TIMP3 post-MI limit infarct expansion, and attenuate LV dilation and dysfunction.

Methods: MI was induced in adult male wildtype (C57BL/6) mice by ligation of the left anterior descending artery. Adenoviral constructs expressing human TIMP3 (Ad-hTIMP3) or no-TIMP (Ad-null, control) were injected in the peri-infarct zone (5.4x10^7 pfu, 5 injections/heart). Cardiac function was assessed by echocardiography. Cardiomyocyte density (WGA/DAPI staining), vascular density (Fluo-lectin injection, CD31 IHC), ECM composition (PSR staining) were assessed at 3 and 7 days post-MI. In vitro, angiogenic potency of TIMP3 (rTIMP3) was assessed using the 3D fibrin gel-based angiogenesis assay using primary human vascular (HUVECs) and coronary artery endothelial cells (HCAECs), and co-IP between TIMP3 and VEGFR2.

Results: Ad-TIMP3 injections significantly improved LV function and reduced LV dilation as compared to Ad-null group post-MI. Infarct size was markedly reduced with TIMP3 injections and more viable myocytes were preserved in the infarct zone at 1wk post-MI. Ad-TIMP3-MI group showed a higher density of endothelial cells and increased coronary density in the infarct and peri-infarct regions compared to the Ad-null group. This suggested that Ad-TIMP3 promotes angiogenesis in the infarcted myocardium. In vitro studies confirmed that rTIMP3 promoted angiogenesis/sprouting in human endothelial cells up to 10ng/ml. However at higher concentrations (>1ug/ml), rTIMP3 exerted anti-angiogenic effects by binding to VEGFR2. This function of rTIMP3 appears to be through an MMP-inhibitory mechanism.

Conclusion: The novel pro-angiogenic function of TIMP3 post-MI could provide additional beneficial effects in post-MI treatment.
HYPEROXIA REDUCES OXYGEN CONSUMPTION IN CHILDREN WITH PULMONARY HYPERTENSION

Long Guo, Karunakar Vadlamudi, Prashant Bobhate, James Coe, Ian Adatia

Background: High inspired oxygen concentration (FiO2) is administered to test pulmonary vasoreactivity in children. Oxygen consumption (VO2) cannot be measured accurately with conventional methods if the inspired FiO2 >0.85 and it is usually assumed that (VO2) does not change with hyperoxia.

Hypothesis: We hypothesised that an inspired FiO2 >0.85 would change VO2 compared with VO2 in room air (RA) and could influence the accuracy of flow calculations using the direct Fick equation.

Methods: We reviewed retrospectively the cardiac catheterization data obtained between 2009-Dec 2015 in children with pulmonary hypertension (PH) without cardiac shunts and cardiac output (CO) measured by thermodilution in 2 conditions like RA, and with an FiO2 >0.85. VO2 was calculated using the Fick equation CO= VO2 / arterial-venous oxygen content difference. Dissolved O2 was included in the calculation.

Results: Data was available in 32 subjects (male=15), median age 8.3 years (IQR 3.0 -11.6), median weight 23.7 kg (IQR 13.3-38.8), BSA median 0.9 m2 (IQR 0.5-1.2 m2). The median indexed VO2 in RA was 140 ml/min/m2 (range 84-238) and decreased in hyperoxia to 129 ml/min/m2 (range 83-230) (p=0.03). The median percentage change in VO2 from RA to FiO2>0.85 was 9% (p=0.007). In 0.86 litres/minute/m2 (p=0.04)

Conclusion: VO2 decreased significantly during hyperoxia in children with PH. If VO2 is assumed to remain constant during hyperoxia errors may be introduced if the direct Fick equation is used to calculate pulmonary and systemic blood flow. The assumption that VO2 remains unchanged in hyperoxia may be incorrect and deserves further investigation especially in children with cardiac shunts.
GENETIC LANDSCAPE OF THE CALCIUM REGULATORY PROTEIN PHOSPHOLAMBAN IN DILATED CARDIOMYOPATHY – FUNCTIONAL UNDERPINNINGS OF HEREDITARY DCM

Gareth Armanious, Jessica Gifford, Catharine Trieber, Howard Young

Background: SERCA achieves the majority of the calcium removal from the cytosol of cardiomyocytes by actively transporting calcium ions from the cytosol into the sarcoplasmic reticulum during diastole. Reversible inhibition of SERCA SR membrane protein phospholamban (PLB) is crucial to controlling the rate of calcium sequestration, and magnitude of the calcium gradient between the sarcoplasm and cytoplasm. This determines the rate of diastole and force of the subsequent contraction. Unphosphorylated PLB decreases SERCA calcium affinity, while β-Adrenergic-mediated phosphorylation of PLB at S16 by PKA, or at T17 by CaMKII restores SERCA activity and increases cardiac output. New mutations in PLB have been recently identified in patients with heart failure. For example, an A15T mutation was identified in a 4 year old female DCM patient, and a P21T mutation in a 60 year old female patient, both with a family history of DCM. Interestingly, the 4-year-old patient also has a mutation in myosin binding protein C3 (MYBPC3) listed as being “likely benign” that may contribute to the surprisingly young age of diagnosis. The effects that these variants of PLB have on the kinetics of SERCA, as well as their implications to the regulation of PLB via phosphorylation by PKA is currently under investigation.

Methods: Recombinantly expressed PLN was purified and co-reconstituted in the presence of SERCA and spectroscopic techniques were used to assess the calcium dependent specific activity of SERCA. The secondary structure of PLN variants was assessed by circular dichroism (CD) to correlate structural changes of PLN with altered PLN-SERCA regulatory complex kinetics. Lastly, the ability for these mutants to be phosphorylated by the catalytic subunit of PKA and then dephosphorylated by PP1 was assessed. Molecular dynamics simulations (MD) are underway to assess the stability of the MYBP mutation.

Results: The P21T variant of PLN showed increased helical content by circular dichroism compared to WT PLN, while the A15T mutation resulted in little to no change in helical content. The inhibitory effects of P21T phospholamban were more potent than those of WT PLN, while the A15T variant of PLN further decreased the apparent calcium affinity of SERCA compared to SERCA in the presence of WT PLN. When these variant of phospholamban were phosphorylated however, their inhibition on SERCA was relieved to a level similar to that of phosphorylated WT PLN. A15T mutation of phospholamban severely decelerates phosphorylation of the regulatory protein, as do other clinical mutations in close proximity to serine 16. MD simulation of MYBP shows decreased stability in the structural domain of the mutation site.

Conclusion: The A15T and P21T variants of PLN resulted in altered inhibitory characteristics compared to WT PLN when in complex with SERCA. The inhibition of SERCA activity was relieved to varying extents when these variants of PLN were phosphorylated compared to WT. The more severe A15T mutation effected adrenergic drive, while the MYBP variant listed as benign showed decreased domain stability. Further analysis of the effects on PP1 recognition and the rate of phosphatase activity on these PLN mutants is currently under investigation to assess the global signaling effects in the myocardium.
CHILDREN WITH HYPOPLASTIC LEFT HEART SYNDROME

Dora Gyenes, Joseph Atallah, Charlene Robertson, Gwen Alton, Irina Dinu, Fahimeh Moradi, Winnie Savard, Lisa Hornberger

Background: Children with hypoplastic left heart syndrome (HLHS) are at increased risk of compromised clinical and neurodevelopmental (ND) outcomes. Placental pathology with an onset likely in the 3rd trimester has been recently found to be a common feature of HLHS. In the present study, we investigate the relationship of umbilical arterial (UA) flow patterns in fetal HLHS to neonatal clinical and 2-year ND outcomes.

Methods: We identified all children with HLHS prospectively followed in the Western Canadian Complex Pediatric Therapies Follow-Up Program who had a fetal echocardiogram in the University of Alberta Fetal & Neonatal Cardiology Program between March 2005 and June 2013. Patients who died prior to 2 years were excluded. Third trimester fetal echocardiograms were analyzed offline, measuring UA-PI ([peak systolic-peak diastolic velocity]/mean velocity). Clinical neonatal and perioperative parameters were assessed around the initial Norwood operation, and Bayley III assessments (cognitive, language, and motor development) at 2 years were reviewed. Univariate and multiple linear regression identified predictors of initial length of hospitalization, 2-year growth and cognition.

Results: Thirty-four children met inclusion criteria. Average gestational age at fetal echo was 39.2 ± 1.4 weeks. The univariate analysis is presented in the table below. On multiple variable analysis, variables associated with length of hospitalization at Norwood included age at surgery, effect size=1.14 (95% CI 1.38, 2.19), p=.005; and UA-PI, effect size=29.17 (95% CI 7.79, 50.56), p=.009, total variance=35.8%. UA-PI contributed to the variance of 2-year weight and head circumference by 28.1% and 9.5% respectively, but not directly to length, cognition, language or motor scores.

Conclusion: Higher UA PI in fetal HLHS was univariately associated with worse clinical perioperative status around the Norwood procedure, 2-year growth and cognitive outcomes. UA-PI accounted for 14% of the variance of length of hospitalization, but other predictors combined to give the other outcomes. Altered umbilical arterial flow possibly secondary to placental pathology may be an added mechanism of insult previously unrecognized in HLHS.

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<th>95% CI</th>
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<td>Birth weight</td>
<td>-1.85</td>
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<td>Pre-operative highest lactate</td>
<td>2.37</td>
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<td>Post-operative ventilation days</td>
<td>8.73</td>
<td>0.96, 16.5</td>
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<td>33.53</td>
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<td>2-year head circumference</td>
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<td>-6.33, -1.29</td>
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<td>2-year weight</td>
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<td>-4.81, -1.38</td>
<td>.001</td>
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<tr>
<td>2-year length</td>
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<td>-4.98, -0.80</td>
<td>.008</td>
<td>17.8</td>
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<tr>
<td>2-year cognitive score</td>
<td>-21.96</td>
<td>-42.67, -1.25</td>
<td>.038</td>
<td>10.3</td>
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</table>
Table 1. Evidence-based medications prescribed at baseline and at the 6 month visit (% of patients).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline (%)</th>
<th>At 6 months (%)</th>
</tr>
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<tbody>
<tr>
<td>ACEI/ARB</td>
<td>86.5</td>
<td>91.5</td>
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<tr>
<td>BB</td>
<td>88.8</td>
<td>99.6</td>
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<tr>
<td>MRA</td>
<td>44.8</td>
<td>62.3</td>
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<tr>
<td>ACEI/ARB + BB</td>
<td>78.5</td>
<td>91.0</td>
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<tr>
<td>ACEI/ARB + BB + MRA</td>
<td>39.9</td>
<td>59.6</td>
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</tbody>
</table>

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist
PHARMACOLOGICAL CHARACTERIZATION OF THE FUNCTIONAL ROLE
OF CALCIUM-ACTIVATED POTASSIUM CHANNELS IN PLATELETS

Valentina Back, Frances Plane, Paul Jurasz

Background: In arteries, stimulation of endothelial cell small (SKCa) and intermediate (IKCa) conductance calcium-activated potassium channels provides a negative-feedback mechanism to limit agonist-induced vasoconstriction. Additionally, endothelial cell KCa channels in conjunction with nitric oxide (NO) mediate vasodilatation in response to agonists and physical stimuli such as increases in blood flow. Platelets, like endothelial cells, possess KCa channels and have the capability to 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 objective was to pharmacologically characterize SKCa and IKCa channel function in platelets, and to investigate their role in platelet NO production. Our hypothesis was that pharmacological activation of KCa channels would inhibit platelet aggregation and enhance platelet NO production.

Methods: Platelets were isolated from the blood of healthy volunteers and aggregometry performed in the presence of SKCa (CyPPA) and IKCa (SKA-31) channel activators. Dense granule secretion was measured by ATP chemiluminescence. DAF-FM flow cytometry was used to measure NO generation.

Results: CyPPA and SKA-31 inhibited collagen-induced aggregation in a concentration dependent manner (control: 75.33±7.21%, vs. CyPPA 10μM 29.67±22.32% and 100μM 2.00±1.15%, N=3, P<0.05) (control: 75.33±8.65% vs. SKA-31 10μM 31.33±11.35% and 100μM 0.33±0.33%, N=3, P<0.05). CyPPA and SKA-31 demonstrated similar inhibitory effects on platelet dense granule secretion (CyPPA 10 μM: 65.74±11.04% reduction, N=4; SKA-31 10μM: 55.30±6.74% reduction, N=5). CyPPA and SKA-31 inhibited NO generation back to basal resting platelet levels. Calcium channel blocker nifedipine (10μM) potentiated the anti-aggregatory effects of 10μM CyPPA and SKA-31 (control 95.23±3.63% vs. CyPPA 79.12±2.87% vs. CyPPA and nifedipine 27.06±14.17%, N=4; control: 95.80±1.60% vs. SKA-31 67.19±10.06% vs. 26.17±13.31% SKA-31 and nifedipine, N=4, P<0.05). IKCa selective channel blocker TRAM-34 reversed the anti-aggregatory effects of 10μM SKA-31 but not CyPPA (control 95.80±1.60% vs. SKA-31 67.19±10.06% vs. 73.69±7.76% SKA-31 and TRAM-34, N=4, P<0.05) (control 95.23±3.63% vs. CyPPA 79.12±2.87% vs. 82.32±3.45% CyPPA and TRAM-34, N=3). SKCa channel-selective blocker apamin did not reverse the effect of either CyPPA or SKA-31 (control 95.23±3.63% vs. CyPPA 79.12±2.87% vs. CyPPA and apamin 65.99±7.10% N=3) (control 95.80±1.60% vs. SKA-31 67.19±10.06% vs. 60.21±9.97% SKA-31 and apamin, N=4).

Conclusion: Activation of SKCa and IKCa channels inhibits both platelet aggregation and platelet NO generation. Furthermore, the use of selective blockers suggests that IKCa is the dominant KCa channel within platelets. These data indicate that KCa channels may provide novel targets for therapeutics to inhibit platelet aggregation.
THE IMPACT OF SOCIAL MEDIA ON CARDIOVASCULAR MEDICINE: INSIGHTS INTO TWITTER’S SPHERE OF INFLUENCE

Pishoy Gouda, Debraj Das, Alex Clark, Justin Ezekowitz

Background: Social media is an increasingly relevant tool used to deliver and receive healthcare related content by both patients and clinicians. Currently, there are >75,000 healthcare providers using Twitter, which allows users to share posts up to a maximum of 140 characters. With the majority of Twitter content available as public data, it provides an opportunity to examine how individuals and organizations interact with specific healthcare keywords (“hashtags” that start with #, e.g. #cardiology).

Methods: We undertook a systematic review of formal health-related studies that evaluated twitter content. Standard systematic review techniques were used and Pubmed and Scopus databases were searched using the keywords: Twitter, medicine, healthcare and cardiology. Studies (2000-2015) had to evaluate Twitter content on one or more healthcare topics. In addition, we evaluated trends in four cardiovascular (CV)-related keywords (#HeartAttack, #Hypertension, #HeartFailure and #AtrialFibrillation) on Twitter. For each hashtag, we conducted an analysis of 100 randomly selected tweets, for a total of 400 tweets.

Results: The final database included 14 descriptive studies; none were CV related. Combined, these articles evaluated over 16 million tweets on a range of topics including: health policy, infectious disease, urogynecology and public health. Using an analytical tool that evaluates Twitter content (Symplur) in March 2016 there were 6,792 mentions of #HeartAttack, 3,492 mentions of #Hypertension, 2,794 mentions of #HeartFailure and 1,952 mentions of #AtrialFibrillation. Combined, these tweets made ~75 million “impressions” (the number of times the tweets were delivered to the streams of individual users; Figure). In our randomly selected sample of tweets, the majority of identified tweets (85.5%) were medically related with tweets from accounts of healthcare organisations, (54.9%), individual healthcare professionals (38.6%) and 6.5% from patients. Tweets provided links to medically related content (51.7%), news articles (29.0%) and peer-reviewed journal articles (19.3%).

Conclusion: Despite a lack of formalized research, social media has become an increasingly powerful tool for knowledge transfer in CV medicine, with many individuals and organizations actively disseminating and/or acquiring information daily. Analyzing publicly available Twitter data will continue to provide valuable insight into public perception of CV diseases and treatments as well as identify opportunities to further engage patients and healthcare providers online.
MICROTUBULE ACETYLATION AND A NEW CELLULAR “HIGHWAY” FOR THE TRANSLOCATION OF METABOLIC ENZYMES FORMS THE BASIS OF A NOVEL METABOLISM-EPIGENETICS AXIS

Sotirios D. Zervopoulos, Aristeides E. Boukouris, Alois Haromy, Adam Kinnaird, Vikram Gurtu, Trevor Stenson, Evangelos D. Michelakis

Background: Microtubules are heterodimers of α- and β-tubulin that span the cytoplasm forming a dynamic network that is dysregulated in both myocardial and vascular disease. Stability of this network has been associated with the acetylation of lysine 40 (K40) of α-tubulin through the opposing actions of α-Tubulin Acetyl-transferase 1 (αTAT1) and Histone de-acetylase 6 (HDAC6). Acetylation of K40 facilitates the binding of motor proteins involved in intracellular protein and organelle trafficking. Our group has shown that the mitochondrial pyruvate dehydrogenase complex (PDC) can translocate to the nucleus and increase global histone acetylation (Cell, 2014) by a yet unidentified mechanism. In addition to cancer cells, the same is true in vascular cells in pulmonary hypertension. Histone acetylation is important for chromatin relaxation and gene transcription. We hypothesized that microtubule acetylation facilitates either mitochondrial translocation around the nucleus (where they can directly “donate PDC”) or the trafficking of PDC-containing vesicles/endosomes toward the nucleus.

Methods: Tubulin acetylation was manipulated by tubacin (a specific HDAC6 inhibitor) or siRNA against αTAT1. Nuclear PDC and α-tubulin acetylation levels were measured by immunostaining (confocal and electron microscopy) and immunoblots. PDC trafficking was monitored in live cells under a confocal microscope after we ectopically expressed a mitochondria-targeted photoactivated GFP or a photoconvertible protein (Dendra2) fused to the E2 subunit of PDC respectively.

Results: Both serum stimulation and hypoxia increased tubulin acetylation and nuclear PDC levels in epithelial cells and fibroblasts. Hypoxia resulted in an increase of perinuclear mitochondrial density. However, this subpopulation of mitochondria exhibited a sliding “kiss-and-run” pattern along the nuclear envelope under exposure to both serum stimulation and hypoxia. Hypoxia also increased nuclear PKM2, a cytoplasmic glycolytic enzyme, which, like PDC, has been described in proliferative diseases and heart failure. Tubacin increased both tubulin acetylation and nuclear PDC under hypoxia and serum stimulation, but did not affect perinuclear mitochondrial clustering. In contrast, αTAT1 silencing decreased tubulin acetylation and nuclear PDC under hypoxia but not serum. Both interventions did not affect nuclear PKM2 levels.

Conclusion: Our data suggest the presence of two pathways for nuclear translocation of mitochondrial proteins. One microtubule-independent mechanism involving direct “donation” of PDC to the nucleus potentially by fusion of nuclear/mitochondrial membranes (similar to how mitochondria fuse to ER membranes). And another, regulated by tubulin acetylation, particularly under hypoxia, involving mitochondrial but not cytoplasmic proteins. Translocation of metabolic enzymes to the nucleus provides the basis of the newly discovered metabolism-epigenetics axis and may facilitate novel drug development in cardiovascular disease.
ALTERED UMBILICAL ARTERIAL BLOOD FLOW IN THE 3RD TRIMESTER AND ITS ASSOCIATION WITH CLINICAL AND NEURODEVELOPMENTAL OUTCOMES IN TARGET DOSE ACHIEVEMENT OF EVIDENCE-BASED MEDICATIONS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION ATTENDING A MULTIDISCIPLINARY HEART FAILURE CLINIC

June Chen, Charlotte Galenza, Finlay McAlister, Justin Ezekowitz, Kaitlin Rafuse, Ann-Marie Sande, Sheri Koshman

Background: Guidelines recommend both angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and beta-blockers (BB) at evidence-based target doses for patients with heart failure (HF) with reduced ejection fraction. Despite utilization of these medications in practice, doses used are often lower than recommended. The objective of this study was to determine the achievement of target or maximally tolerated doses of both ACEI/ARB and BB within 6 months of entering a multidisciplinary HF clinic.

Methods: A retrospective chart review was conducted on consecutive patients attending the Mazankowski Alberta Heart Institute’s Heart Function Clinic from October 2012 to February 2015 with a LVEF < 45%. Exclusion criteria were: pregnancy, <2 encounters in 12 months, at target doses of both an ACEI/ARB and BB at clinic entry, and being ineligible for either medication at the first clinic visit. Target dose was selected from the CCS HF guidelines with the lower dose being used if a range was provided. Maximally tolerated dose was as documented in the medical record or documentation of the highest dose of medication that the patient or healthcare provider would take or prescribe due to adverse effects.

Results: Of the 359 records screened, 223 (62%) patients were included. The median age was 67 years, 77% were male, median LVEF was 27 (18.5-34) %, and 87%, 89% and 45% were prescribed an ACEI/ARB, BB and/or mineralocorticoid receptor antagonist (MRA) at clinic entry, respectively. Within 6 months of clinic entry, achievement of target or maximally tolerated doses increased from baseline (Figure 1). In those not reaching target or maximally tolerated doses, 81% and 61% had a documented reason for the ACEI/ARB and BB, respectively. Low blood pressure and improved LVEF were the most common reasons documented. In the ACEI/ARB group without a documented reason, the median SBP was 120 (107-121) mmHg, potassium was 4.6 (4.5-4.8) mmol/L and serum creatinine was 100 (81.5-116.5). For the BB group, the median HR was 66 (60-71.75) bpm and SBP was 121 (116-138) mmHg. Overall, total utilization of evidence-based medications, including triple therapy with a MRA, increased from baseline to 6 months (Table 1).

Conclusion: The achievement of target or maximally tolerated doses of both ACEI/ARB and BB increased within 6 months of entering a HF clinic, but remained low overall. Although the majority of patients had documented reasons for not achieving target doses, there remained a proportion with suboptimal up-titration, especially of BB.
**ACUTE PHARMACOLOGICAL INHIBITION OF PI3Kα BY BYL-719 HAS A PRO-ARRHYTHMIC EFFECT IN MURINE HEARTS**

Pavel Zhabyeyev, Brent McLean, Bart Vanhaesebroeck, Gavin Y. Oudit

**Background:** Phosphatidylinositol-3-kinase α (PI3Kα) is a highly important therapeutic target because this kinase has high activity in many cancer types. BYL-719 (BYL) is a specific PI3Kα inhibitor (IC50 of 5 nM) and a prospective cancer drug for advanced solid tumors. However, the potential of BYL for adverse electrophysiological effects on the heart is unclear.

**Methods:** In isolated cardiac myocytes, contractility was assessed by sarcomere tracking, sarcoplasmic Ca2+ release was measured using fluorescent dye FURA 2, and electrical activity was recorded using patch-clamp techniques: current-clamp mode was used for action potentials, and voltage clamp mode was used for K+, Ca2+, and Na+ currents. In excised hearts, electrical activity and Ca2+ release were visualized using epicardial optical mapping with fluorescent probes for voltage (RH237) and Ca2+ (Rhod-2). In vivo cardiac electrical activity was assessed using electrocardiography. PI3Kα-deficient mice (MHCα-Cre-p110αflx/flx) were used as a negative control to confirm specificity of BYL action on PI3Kα.

**Results:** In isolated cardiac myocytes, BYL increased contractility in a dose-dependent manner (1 µM BYL increased fractional shortening (FS) by 27.8 ± 7.2%). Sub-maximal concentration of 100 nM was used for the study (FS increased by 24.0 ± 6.5%). BYL failed to increase contractility in PI3Kα-deficient mice or when BYL was applied with specific reverse-mode Na+/Ca2+ exchanger (NCX) blocker (3 µM KB-R7943) or ranolazine (10 µM), which blocks both reverse mode NCX and late Na+ current (I_{Na,L}) suggesting PI3Kα-dependent effect mediated via NCX with possible I_{Na,L} involvement. BYL increased Ca2+ release by 20.9 ± 5.7%. This increase was absent in PI3Kα-deficient mice and was blocked by ranolazine. BYL prolonged action potential at 20, 50, and 90% of repolarization by 11.0 ± 2.2%, 16.1 ± 2.2%, and 10.5 ± 2.2%, respectively. Similar to contractility and Ca2+ release, prolongation of action potential was absent in PI3Kα-deficient mice and was blocked by ranolazine. Investigation that BYL did not affect K+ currents, but inhibited L-type Ca2+ current and activated late Na+ current in PI3Kα-dependent manner. In whole heart preparations, action potential was prolonged and Ca2+ release was increased in a manner similar to isolated myocytes. Administration of BYL to wild-type mice for 4 days prolonged QT interval: QT_{cB} (Bazett) increased by 16.7 ± 3.9% and QT_{cF} (Fridericia) increased by 19.4 ± 4.4%. Other intervals (RR, QRS, and PR) were not significantly affected. PI3Kα deficient mice lacked the increase in QT interval in response to BYL treatment.

**Conclusion:** Acute pharmacological inhibition of PI3Kα activity by BYL has a pro-arrhythmic effect (prolongation of QT interval). The prolongation of QT interval arises from prolongation of action potential driven by late Na+ current and NCX activity. Activation of late Na+ current and NCX activity have a concomitant effect of increased Ca2+ load of the sarcoplasmic reticulum (potentially pro-arrhythmic) and increased contractility of cardiac myocytes. Pro-arrhythmic effects of BYL (increased Ca2+ load and prolongation of action potential) were abolished by ranolazine.
COMPARISON OF LEFT VENTRICULAR MAXIMUM STRAIN TO EJECTION FRACTION MEASUREMENTS FROM CONVENTIONAL CINE CARDIAC MAGNETIC RESONANCE IMAGES

Jiali Luan, Richard Thompson, Ian Paterson, Kumaradevan Punithakumar, Michelle Noga

**Background:** Left ventricular systolic heart function is frequently evaluated by measuring left ventricular ejection fraction (LVEF), based on conventional cine cardiac MRI (CMR). Endocardial strain has been proposed as an alternative measure for evaluating systolic dysfunction. The objective is to compare strain from CMR analysis with LVEF as an alternative, more robust measure of systolic function.

**Methods:** 127 patients at risk for heart failure and normal volunteers were recruited for CMR scanning. Two, 3 and 4 chamber long axis longitudinal strains as well as short axis (SA) circumferential strains were calculated from the length change of LV endocardial contours on cine MR. Global circumferential strain was calculated from the global LV stack as was average circumferential strain from three representative (basal, mid and apical) short axis oblique (SAO) slices. Unweighted average strains were calculated for the sets: 2 and 4 chamber, 3 slices SA and 4 chamber, and 3 slices SA and 2 chamber. A weighted average strain with the relative weights of 50% 3 slices SA, 25% 4 chamber and 25% 2 chamber strains were also calculated. Pearson’s correlation and Bland-Altman analysis were used to assess strain’s correlation to LVEF. Ejection fraction was measured by an independent expert user manually tracing SAO contours on Siemens Argus software. Receiver operating characteristic (ROC) curve analysis was used to determine maximum strain’s ability to detect systolic dysfunction. Maximum strain from global SA, 3 slices SA and LV 4 chamber scans from 10 random subjects were assessed by two observers for inter-observer studies. The intra-class correlation coefficient was used to assess inter-observer reliability.

**Results:** Table 1 shows the results for the Pearson’s correlation. Furthermore, when we compared the 3 slices SA with global SA maximum strain using Bland-Altman analysis, we found a bias of 0.11 and limits of agreement from -3.4 to 3.2. LVEF as a function of global and 3 slices SA strains are LVEF = -1.98(X_{global}) + 7.64 and LVEF = -2.02(X_{3 slice}) + 6.59. The intra-class correlation coefficient is 0.88 for global SA, 0.54 for 3 slices SA and 0.71 for LV 4 chamber strains. The area under the ROC curve for global SA and 3 slices SA are 0.97 and 0.96 respectively. Furthermore, absolute value maximum strain cutoffs for systolic dysfunction are strain<22.39 for global SA and strain<22.86 for 3 slices SA.

**Conclusion:** Maximum strain measurements from cine CMR SA scans correlate well with LVEF to provide a reliable alternative measure of systolic function.

Table 1 Pearson’s correlation coefficients

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<tr>
<th>Scan view</th>
<th>Pearson’s r compared with LVEF (absolute value)</th>
</tr>
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<td>Short axis global stack</td>
<td>0.93</td>
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<tr>
<td>Short axis three representative</td>
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<tr>
<td>Three slices, four and two chamber average</td>
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<td>Three chamber</td>
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<tr>
<td>Two and four chamber average</td>
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<tr>
<td>Four chamber</td>
<td>0.58</td>
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METABOLIC MODULATION AS A NOVEL THERAPY IN CHEMOTHERAPY INDUCED CARDIOTOXICITY
Bruno Saleme, Adam Kinnaird, Aristeidis Boukouris, Sotirios Zervopolous, Vikram Gurtu, Gopinath Sutendra

Background: Chemotherapy Induced Cardiotoxicity (CIC) is a serious complication that results in early termination of cancer therapies, despite responsive tumors. There are no therapies to prevent CIC, as our understanding of the mechanisms in this condition is limited. Intriguingly, similar metabolic processes (increased glycolysis) has been described in heart failure and cancer, suggesting metabolic therapies may be beneficial against both diseases. One challenge in designing CIC therapies is protecting the heart against apoptosis without hindering chemotherapy-mediated tumor apoptosis. An intriguing difference between the myocardial and tumor microenvironments is the former is normoxic (oxidized) and the latter hypoxic (reduced), suggesting that targeting metabolic redox-sensitive proteins induced by chemotherapy agents in the heart may provide selectivity against CIC, without compromising tumor suppression. We hypothesized that cardiotoxic agents induce the inactive form of the metabolic redox-sensitive protein pyruvate kinase-M2 (PKM2) in the heart and therapeutic activation may prevent CIC.

Methods: Cell lines: H9c2, A549; Reagents: Adriamycin, TEPP-46, H$_2$O$_2$, diamide, DTT; Techniques: immunoblots and confocal (apoptosis: caspase-3/TUNEL/Bax/p21); in-vivo: xenotransplanted mice with tumors were randomized/treated for 14 days with vehicle, TEPP-46, Adriamycin or Adriamycin+TEPP-46.

Results: The cardiotoxic agent Adriamycin induced the inactive form of PKM2 in H9c2 cardiomyocytes in both normoxia and hypoxia. Adriamycin-mediated apoptosis in H9c2 was inhibited by the PKM2 activator TEPP-46 in an oxidized (normoxia, H$_2$O$_2$, diamide), but not reduced (hypoxia, DTT) environment, and additionally increased apoptosis in A549 (pseudohypoxic) cancer cells. Furthermore, activation of oxidized, but not reduced PKM2 by TEPP-46 resulted in inhibition of the pro-apoptotic transcription factor p53. In-vivo, Adriamycin induced the inactive form of PKM2 and increased apoptosis in the myocardium, and this was inhibited by TEPP-46, which further decreased lung tumor size in xenotransplanted mice (Figure).

Conclusion: Our novel data provide the first evidence that redox-targeted metabolic therapies are beneficial against CIC, while synergistically decreasing tumor growth.
Figure. PKM2 Activators As A Novel Therapy In Chemotherapy-Induced Cardiotoxicity

(A) The PKM2 activator TEPP-46 inhibits Adriamycin-mediated apoptosis (as assessed by cleaved caspase-3) in H9c2 cardiomyocytes in normoxia (i.e. oxidized), but not hypoxia (i.e. reduced). TEPP-46 enhances Adriamycin-mediated apoptosis in A549 cancer cells (i.e. reduced). Actin was used as a loading control.

(B) TEPP-46 treatment partially prevents Adriamycin-induced apoptosis (TUNEL in green) in the myocardium (MHC+ cells; not shown) of xenotransplant mice with human tumors, protecting against decreased cardiac function.

(C) TEPP-46 enhances Adriamycin-mediated tumor suppression assessed by tumor volume and size.
ASSOCIATION BETWEEN 24/7 INTENSIVIST-ONLY MANAGEMENT AND POST-OPERATIVE COMPLICATIONS, RESOURCE UTILIZATION AND OUTCOMES AMONG CARDIAC SURGERY PATIENTS: A PROPENSITY MATCHED COHORT STUDY

Marc Benoit, Sean M Bagshaw, Colleen M Norris, Mohamad Zibdawi, W.D. Chin, David B Ross, Sean van Diepen

Background: Night-time intensivist staffing does not improve patient outcomes in general medical or surgical intensive care units. To date, few studies have examined the association between dedicated in-house 24/7 intensivist coverage on post-operative complications, health service utilization, and outcomes in specialized cardiovascular surgical intensive care units (CSICU).

Methods: In a before and after study design linked to the withdraw of resident nighttime coverage from a tertiary CSICU, patients ≥ 18 years who underwent cardiac surgery between January 1, 2006 to April 30, 2013 (nighttime resident model) were propensity matched (1:1) to patients from August 1, 2013 to December 31, 2014 (24/7 in-house intensivist model). The primary outcome was a composite of post-operative major complications. Secondary outcomes were duration of mechanical ventilation, CSICU length of stay (LOS), all-cause CSICU readmission, and surgical cancellations attributed to lack of CSICU bed availability.

Results: In total, 1,509 patients during the nighttime resident model were matched to 1,509 patients during the 24/7 in-house intensivist model. The adjusted risk of major complications (26.3% vs 19.3%; Odds Ratio [OR] 0.67; 95% CI, 0.56-0.80, p<0.001; Figure), mean mechanical ventilation time (25.2 vs 19.4 hours, p<0.001), CSICU readmission (5.3% vs 1.6%, OR 0.52; 95% CI, 0.30-0.90, p<0.001), and surgeries postponed due to lack of CSICU beds (3.4 vs 0.3 per month, p<0.001) were all significantly lower with the 24/7 intensivist model. No differences were observed in CSICU LOS (4.98 vs 5.01 days, p=0.89) or 30-day mortality (3.1 vs 3.6%; OR: 0.80; 95% CI 0.49-1.31, p=0.41).

Conclusion: A 24/7 in-house intensivist care model is associated with a reduced incidence of post-operative major complications, duration of mechanical ventilation, CSICU readmissions, and surgical cancellations due to CSICU bed availability. These findings suggest 24/7 intensivist physician care models may improve patient outcomes and health service utilization in specialized CSICUs.
Figure: Clinical outcomes stratified by nighttime resident coverage and in-house 24/7 intensivist staffing models.

<table>
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<th>Any complication</th>
<th>Resident</th>
<th>Intensivist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>8.8%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Prolonged mech vent</td>
<td>17.2%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Superficial sternal infection</td>
<td>3.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Deep sternal infection</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Vein harvest site infection</td>
<td>2.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>CSICU mortality</td>
<td>1.9%</td>
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</tr>
<tr>
<td>30 day mortality</td>
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<td>3.6%</td>
</tr>
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</table>

Adjusted OR (95% CI)
BASIC SCIENCE POSTERS
Background: Maturational changes in cardiac energy metabolism is characterized by a rapid increase in fatty acid oxidation following birth. However, cardiac hypertrophy, that occurs secondary to a number of congenital heart diseases (CHDs), delays this normal maturation of fatty acid oxidation, thereby decreasing energetic capacity and increasing the susceptibility of the heart to ischemic injury during surgery to correct CHDs. Recently, increased cardiac acetylation has emerged as an important post-translational modification that increases fatty acid oxidation. However, what effect cardiac hypertrophy has on the acetylation control of the maturational change in energy metabolism remains to be elucidated.

Methods: Right ventricular biopsy samples were collected from neonatal patients undergoing corrective surgery for CHDs, and were stratified according to patient age (0-20, 21-100, and 101-200 days), as well as the absence or presence of hypertrophy, (assessed by echocardiography). These samples were further processed for examining energy metabolic enzymes and their acetylation status.

Results: A total of 145 myocardial samples were obtained, and amongst these, 58 samples were from patients in 0-20 days, 41 from 21-100 days, and 46 from 101-200 days of age. Of 145 samples, 62 samples were identified as originating from hypertrophic hearts. Western blot analysis showed that there was a maturational increase in overall myocardial protein acetylation following age in non-hypertrophied hearts. In contrast, this increase in acetylation was not observed in hypertrophied hearts, which was accompanied by an increase in mitochondrial deacetylase SIRT3 expression. Protein expression of fatty acid oxidation enzymes, including long chain acyl CoA dehydrogenase (LCAD) and β-hydroxyacyl CoA dehydrogenase, were unaltered with age, while an age-dependent increase in acetylated LCAD was observed only in the non-hypertrophied hearts. An age-related increase in the expression of malonyl-CoA decarboxylase (MCD), an enzyme important in controlling fatty acid oxidation, was observed in both the absence and presence of cardiac hypertrophy. This was accompanied by an increased expression of the mitochondrial transcriptional regulator PGC-1α. Interestingly, acetylation of PGC-1α decreased with age only in non-hypertrophied hearts, concomitant with decreased expression of the nuclear acetyltransferase GCN5 and nuclear deacetylase SIRT6. No age-dependent change in the expression of hypoxia-inducible factor-1α (HIF-1α) was seen in either group; although an age-related increase in acetylation of HIF-1α was observed in hypertrophied heart samples.

Conclusion: The presence of cardiac hypertrophy in CHDs patients prevents the normal increase in myocardial acetylation following birth, resulting in a delayed maturation of fatty acid oxidation with an increased glycolysis.
CHF-BAS-1

MYOCARDIAL MATRIX METALLOPROTEINASE-2 ACTIVATION CONTRIBUTES TO DOXORUBICIN-IMPAIRED CALCIUM TRANSIENTS IN CARDIAC MYOCYTES

Brandon Y.H. Chan, Bryan G. Hughes, Andrej Roczkowsky, Klaus Ballanyi, Ramses Ilarraza, Richard Schulz

Background: Anthracyclines, such as doxorubicin (DXR), are effective antineoplastic agents prescribed in many cancer chemotherapeutic regimens. However, their therapeutic utility is limited by severe cardiotoxicity. The mechanism of DXR cardiotoxicity is not fully understood, but two key characteristics are elevated oxidative stress and impaired Ca\(^{2+}\) signaling due to decreased intracellular Ca\(^{2+}\) release, a key component of excitation-contraction coupling. Elevated oxidative stress can activate matrix metalloproteinase-2 (MMP-2), a protease our group has shown to cleave sarcomeric proteins and Ca\(^{2+}\) regulatory proteins. We hypothesize that MMP-2 plays a role in DXR cardiotoxicity by proteolyzing these proteins upon activation by oxidative stress, resulting in impaired Ca\(^{2+}\) signaling and cardiac contractile function.

Methods: Neonatal rat ventricular myocytes (NRVM) were treated with 0.5μM DXR in presence or absence of MMP inhibitors ARP-100 or ONO-4817 for up to 24h.

Results: DXR caused no cell death in NRVM, but, as expected, caused necrosis in 15% of human fibrosarcoma HT1080 cells. By 12h of DXR treatment, NRVM exhibited twofold increase in MMP-2 protein levels, and threefold increase in its intracellular activity, relative to vehicle control. ARP-100 or ONO-4817 attenuated DXR-increased MMP-2 activity by 60%. 24h DXR reduced levels of a known MMP-2 target, troponin I, by 40% through a MMP-2-independent mechanism. The effect of DXR-induced MMP-2 activation on intracellular Ca\(^{2+}\) transients was visualized in live NRVM using confocal microscopy and the Ca\(^{2+}\)-binding dye Fluo-8L AM. 24h DXR decreased the amplitude of Ca\(^{2+}\) transients by 72% and 63% under basal and isoproterenol-stimulated conditions, respectively. DXR also reduced the frequency of both basal and stimulated Ca\(^{2+}\) transients by 73%. ARP-100 restored both the DXR-reduced amplitude and frequency of Ca\(^{2+}\) transients. To identify possible targets of DXR-impaired Ca\(^{2+}\) transients, myocytes were perfused in nifedipine and/or thapsigargin, 10µM each. Nifedipine (L-type Ca\(^{2+}\) channel inhibitor) blocked Ca\(^{2+}\) transients under both basal and isoproterenol-stimulated conditions. Whereas thapsigargin (SERCA inhibitor) only prevented Ca\(^{2+}\) transients under isoproterenol-stimulated conditions. These results suggest L-type Ca\(^{2+}\) channel and/or SERCA may be targeted by MMP-2 in DXR-treated NRVM.

Conclusion: At a clinically relevant concentration, DXR activates myocardial MMP-2 in NRVM, which impairs spontaneous intracellular Ca\(^{2+}\) release in cardiomyocytes. This study provide mechanistic insight into the role of MMP-2 in DXR cardiotoxicity, and support the potential for clinical use of MMP inhibitors as prophylactic therapy for patients receiving DXR chemotherapy.
CHF-BAS-2

PI3Kα REGULATES BIOMECHANICAL STRESS-INDUCED CYTOSKELETAL REMODELING: A CRITICAL ROLE OF GELSON IN HEART FAILURE


Background: Biomechanical stress and cytoskeletal remodeling are key determinants in pressure overload-induced heart failure. Class Ia phosphoinositide 3-kinases (PI3Ks) mediate a variety of cellular activities, in response to agonist binding to cell-surface receptors, by generating the phosphatidylinositol (3,4,5)-trisphosphate (PIP3) phosphoinositide lipid. Gelsolin is a Ca2+- and phosphoinositide-regulated actin filament severing and capping protein that is upregulated in failing human hearts and animal models of heart failure. We hypothesize that PI3Kα regulates cytoskeletal remodeling through PIP3-mediated regulation of gelsolin. In addition, loss of gelsolin could attenuate the adverse cytoskeletal remodeling and result in increased resistance to the development of heart failure in response to pressure-overload.

Methods and Results: Loss of p110α kinase activity, in two different transgenic models (PI3Kα dominant-negative (PI3KαDN) and cardiomyocyte-specific PI3Kα-null), resulted in dilated cardiomyopathy and markedly worsened cardiac dysfunction in response to transverse aortic constriction-induced pressure overload. Increased levels of mechanosensor proteins along with decreased F/G-actin ratio exhibited an uncoupling between cardiac mechanotransduction and cytoskeletal remodeling in p110α-null mice. Gelsolin activity was markedly increased in the p110α-null hearts in response to pressure-overload, whereas loss of gelsolin in PI3KαDN/gelsolin-null double mutant mice prevented the adverse cytoskeletal remodeling and preserved the cardiac function. In a murine model of chronic heart failure, loss of gelsolin prevented the pressure overload-induced cardiac dysfunction, fibrosis, and impaired cardiomyocyte contractility resulting in increased survival. Loss of gelsolin also mitigated the biomechanical stress-induced adverse cytoskeletal remodeling, via the attenuation of actin severing activity.

Conclusion: We have identified a novel role of gelsolin as a mediator of adverse cytoskeletal remodeling leading to heart failure, where PI3Kα is a key negative regulator of gelsolin activity.
T-CELL DEPENDENCE OF ANTIBODY RESPONSE TO BLOOD GROUP A-ANTIGEN
Ibrahim Adam, Bruce Motyka, KeSheng Tao, Lori West

**Background:** ABO-incompatible heart transplantation (ABOi HTx) is safe during infancy and allows increased access to donors. B-cell tolerance develops to donor A/B antigen(s) (Ag) following ABOi HTx, but mechanisms of tolerance are not well-defined. Using recently developed A-transgenic (A-Tg) mice (B6 background) expressing human A-Ag on vascular endothelium and erythrocytes (RBC), we investigated the role of CD4+ T-cells in anti-A antibody (Ab) production.

**Methods:** Wild-type C57BL/6 mice (WT) were injected i.p. x3, 1 week apart with human blood group A RBC (hu-A) with (n=3) and without (n=6) CD4-depleting mAb (GK1.5), or A-Tg RBC (n=12) and adjuvant. Anti-A Ab in serum was measured by hemagglutination and ELISA (both IgG and IgM). Four weeks later, A-Tg RBC-injected mice were injected i.p. with hu-A-RBC; anti-A was measured again. To study the effect of human RBC-antigens, human group O (hu-O) and A-Tg RBC were mixed, injected i.p. x3, 1 week apart (n=5), then anti-A IgM titer was measured.

**Results:** Injection of hu-A RBC induced abundant anti-A Ab production (median titer 1:512). Following CD4+ T cell depletion, hu-A RBC injection failed to elicit anti-A Ab (titer <1:4). Despite comparable A-Ag expression, A-Tg RBC did not induce anti-A Ab (median titer ≤1:2), however, injection of hu-A RBC 4 weeks after A-Tg RBC injection elicited abundant anti-A Ab (median titer 1:256). Co-injection of A-Tg and hu-O RBC did not induce anti-A Ab (titer ≤1:2).

**Conclusion:** Administration of A-Ag alone (A-Tg RBC) did not stimulate an anti-A Ab response. This cannot be interpreted as tolerance because subsequent administration of hu-A RBC elicited anti-A Ab. In contrast, hu-A RBC (A-Ag plus foreign glycoproteins/glycolipids) induced a strong anti-A Ab response that was T cell-dependent. The lack of an anti-A response following co-injection of A-Tg RBC and hu-O RBC is consistent with a requirement for a chemical linkage of foreign protein/lipid with A-antigen. Contrary to accepted understanding, this study indicates that A/B Ags alone do not stimulate B cell responses without CD4+ T cell participation.
ASSESSMENT OF NEONATAL TOLERANCE TO BLOOD GROUP A-ANTIGEN IN A MOUSE MODEL OF ABO-INCOMPATIBLE HEART TRANSPLANTATION (ABOi HTX)

Brendon Lamarche, Bruce Motyka, Katrina Labonte, Szu-I Wang, Jean Pearcey, Kesheng Tao, Michael Mengel, Banu Sis, Peter J. Cowan, Lori J. West

Purpose: ABOi HTx can be performed safely in infants due to lack of natural anti-A/B antibodies (Ab), in contrast to adults. Following ABOi HTx, B cell tolerance to donor A/B blood group antigen(s) develops by mechanisms not well understood; for detailed study we developed a mouse model using mice transgenic for expression of human A-antigen as donors (A-Tg, C57BL/6 (B6) background) and B6 wild-type (WT) mice as recipients. We showed that A-Tg heart grafts undergo antibody-mediated rejection (AMR) in adult WT mice with preformed anti-A Ab, whereas A-Tg HTx into WT mice at 4 weeks of age (without preformed anti-A Ab) results in tolerance to A-antigen. The present study investigated whether tolerance can be induced in neonatal WT mice following administration of A-antigen in a form other than a transplant.

Methods: Neonatal WT mice (< 24 hours of age) were injected intravenously with A-antigen expressing splenocytes or splenocytes/bone marrow cells (n=17) from adult A-Tg mice, or left untreated (n=15). At 7 weeks of age, all WT mice were intraperitoneally injected with human A-erythrocytes weekly until week 11; at 13 weeks of age, WT mice (neonatal-treated, n=9; and untreated, n=6) received heterotopic HTx from A-Tg donors. Grafts were monitored for function (beating) and assessed for AMR by histology 14-21 days post-Tx or when beating ceased; serum anti-A Ab was assessed by hemagglutination.

Results: Serum anti-A Ab levels were high in all untreated mice (median titre 1:1024) and low/undetectable in neonatal-treated mice (median titre ≤1:2); anti-human non-A erythrocyte antibodies (3rd party) were present in both groups. In untreated mice 5 of 6 grafts survived, whereas all (9/9) grafts survived in treated mice. Immunophenotypic features (C4d deposition) of AMR were present in 3/6 grafts in untreated mice and in no grafts (0/9) in treated mice. Morphologic evidence of AMR was present in 4/6 grafts in the untreated mice and in 6/9 grafts in treated mice.

Conclusion: The inability to elicit abundant anti-A Ab in neonatal-treated mice suggests that A-antigen specific tolerance was induced by exposure of neonates to A-expressing cells. In contrast, the presence of morphologic AMR in A-Tg grafts (but in the absence of C4d and serum anti-A Ab) of neonatal-treated mice suggests incomplete tolerance to A-antigen. This model will prove useful for addressing mechanisms of tolerance in ABOi Tx.
CHF-BAS-5
ADVANCED IRON-OVERLOAD CARDIOMYOPATHY IN A GENETIC MURINE MODEL IS RESCUED BY RESVERATROL THERAPY
Subhash, Das, Pavel Zhabyeyev, Ratnadeep Basu, Vaibhav Patel, Zamaneh Kassiri, Jason Dyck, Gavin Y. Oudit

Background: Iron-overload cardiomyopathy is prevalent on a worldwide basis and is a major co-morbidity in patients with genetic hemochromatosis and secondary iron-overload. Therapies are limited in part related to the lack of a valid pre-clinical model which recapitulates advanced iron-overload cardiomyopathy.

Methods: Male hemojuvelin knockout (HJVKO) mice were fed with high iron diet (Prolab®RHM 3000 with iron 380 ppm) starting at 4 weeks of age for a duration of 1 year. Aging coupled with high iron diet treatment can lead to an advanced pre-clinical iron-overload cardiomyopathy murine model, which recapitulates genetic iron-overload cardiomyopathy in humans. The resveratrol polyphenol was given at 280 mg/kg/day by oral gavage for last three months.

Results: Aged HJVKO mice in response to iron-overload showed increased myocardial iron deposition and mortality. Our aging studies with the HJVKO mice revealed progressive heart disease oxidative stress, and myocardial fibrosis resulting in heart disease and resulting in advanced iron-overload cardiomyopathy. Echocardiography and invasive pressure-volume loop analyses revealed a complete normalization of iron-overload mediated diastolic and systolic dysfunction in response to resveratrol therapy. Resveratrol therapy (240 mg/day), initiated at 9 months of age and continued until 1 yr of age, resulted in complete normalization of systolic and diastolic dysfunction. Myocardial SERCA2a levels were reduced in iron-overloaded hearts and resveratrol therapy restored SERCA2a levels and suppressed upregulation of NCX1 levels. Iron-mediated oxidative stress and myocardial fibrosis were suppressed by resveratrol treatment with concomitant activation of the phospho-Akt and phospho-AMPK signaling pathways.

Conclusion: A combination of aging and high-iron diet in male HJVKO mice results in a valid pre-clinical model and recapitulates iron-overload cardiomyopathy in humans. Resveratrol represents a feasible therapeutic intervention to reduce the burden from iron-overload cardiomyopathy at advanced stages of iron-overload.
TARGETING ENDOPLASMIC RETICULUM STRESS WITH 4-PHENYLEN BUTYRATE IMPROVES MITOCHONDRIAL METABOLISM AND LUNG FUNCTION IN PULMONARY FIBROSIS

Vikram Gurtu, Roxane Paulin, Christopher White, Adam Kinnaird, Aristeidis Boukouris, Sotirios Zervopoulos, Trevor Stenson, Darren Freed, Jayan Nagendran, Evangelos Michelakis

Introduction: Idiopathic pulmonary fibrosis (IPF) is a deadly disease that can lead to significant hypoxia, pulmonary hypertension and right-heart failure. Early data suggest that the hyper-proliferating fibroblasts of IPF are characterized by a) a cancer-like suppression of mitochondria that promotes proliferation and inhibits apoptosis and b) endoplasmic reticulum stress (ERS). We have shown that ERS suppresses mitochondria by decreasing mitochondrial calcium. We hypothesized that the natural chemical chaperone 4-phenylbutyrate (PBA), an ERS inhibitor, will be beneficial in IPF.

Methods: We studied 2 models: a mouse IPF model (intra-tracheal bleomycin) and human IPF lungs explanted from transplant recipients, immediately studied with ex vivo lung perfusion (EVLP): bronchi connected to a ventilator; pulmonary arteries perfused with recirculating modified Krebs-Henseleit buffer. We studied control, bleomycin, and treated mice receiving PBA in drinking water 2 weeks after bleomycin. We measured lung compliance/elastance (Flexivent platform) and fibrosis (histology). For EVLP we studied 5 IPF lungs, measuring mitochondrial respiration (Seahorse analyzer) and indices of ERS (immunoblots) before/after 1-hour treatment with 4-PBA.

Results: Static pulmonary elastance was increased in bleomycin compared to control mice (24.9 vs 13.3cmH2O/mL) but reduced in PBA-treated mice (16.1cmH2O/mL). Fibrotic grade was also reduced in PBA-treated mice lungs. PBA also decreased ERS in fibroblasts isolated from human lungs in vitro. In EVLP IPF lungs, 4-PBA increased O2 consumption in 3 of the IPF lungs by 30-72% increase.

Conclusion: Chronic 4-PBA treatment can improve lung function in pulmonary fibrosis by limiting ERS and mitochondrial inhibition in mice and at least in some IPF patients. IPF is a multifactorial complex disease and the mitochondria-ERS axis may not be important in all patients. Exploration of this variability will allow precision-medicine approaches in future trials with 4-PBA, a drug that has already been used in clinical trials (diabetes). Human EVLP is an ideal platform in which to study drug responses and biomarkers prior to clinical translation.
IMPROVED LUNG FUNCTION USING A CELLULAR BASED PERFUSATE ON EX VIVO LUNG PERFUSION

Nader Aboelnazar, Sayed Himmat, Sanaz Hatami, Christopher White, Vishnu Vasanthan, Jessica Luc, Jaskiran Sandha, Darren Freed, Jayan Nagendran, Jayan Nagendran

Background: The number of donor lungs for transplantation continues to be in shortage due to the fact that <25% of lungs being donated are accepted for transplantation. Ex-vivo lung perfusion (EVLP) is used to “resuscitate” donor lungs improving their suitability for transplantation. Nonetheless, EVLP is clinically limited to 4-6 hours. Furthermore, there is a discrepancy in literature towards the “optimal” perfusate composition that should be utilized, which will extend the perfusion window safely and allow for further resuscitative targeted therapies (including cell and gene therapies).

Objectives: Investigating which perfusate composition will further extend perfusion safely to 12 hours without diminishing lung function. Moreover, any differences with perfusate specific composition in leukocyte and/or edema formation throughout the perfusion.

Methods: Using a custom-made, fully automated, and portable EVLP platform, 18 porcine lungs (37-47kg) were individually perfused for 12 hours. Three treatment/perfusate groups: 1. STEEN solution™ (n=6), 2. packed Red Blood Cells (pRBCs) + STEEN solution™ (n=6) and 3. Whole Blood + STEEN solution™ (n=6). Every two hours, physiological parameters were recorded, a perfusate sample taken (for ELISA analysis of TNFa, IL-6, IL-8, and IL-10), and a hypoxic pulmonary vasoconstriction (HPV) challenge conducted: for assessment of vascular function and integrity.

Results: Lung oxygenation (P/F [Pulmonary venous pO2/Fraction of inhaled oxygen]) remained acceptable (>400 mmHg), along with stable physiological parameters for 12 hours on our EVLP platform. At 7 hours, the lungs demonstrate maximal hypoxic pulmonary vasoconstriction (HPV) across all three perfusates, with pRBCs+STEEN showing the greatest increase in pulmonary vascular resistance of 597±127 dyn*s/cm5. However, beyond the 7th hour of perfusion, HPV was blunted. Interestingly, there is an ongoing accumulation of pro-inflammatory cytokines, in parallel with the decrease in HPV in all three groups. Finally, the acellular perfusate showed an 80±18% in weight gain, whole blood (22.4±7.7%), and pRBCs (25.6±7%), p<0.01, after 12 hours.

Conclusion: Established a reproducible EVLP technique up to 12 hours with stable physiological parameters - extending the limited perfusion window. HPV challenge is a more sensitive index of lung health than the current standard (P/F ratio). Lastly, cellular perfusates demonstrate superior vascular function and integrity (50% less edema) over acellular perfusates. Targeted anti-inflammatory strategies may allow significant extension of the EVLP with direct clinical implications.
CVS-BAS-2

DOES A LEUKOCYTE FILTER SHOW BENEFIT IN EX-VIVO LUNG PERFUSION?

Jessica G.Y. Luc, Nader Aboelnazar, Sanaz Hatami, Alois Haromy, Vishnu Vasanthan, Christopher W White, Darren H Freed, Jayan Nagendran

Background: Lung transplantation is limited by a shortage of donor lungs. Normothermic ex vivo lung perfusion (EVLP) is a technology that allows for assessment and reconditioning of donor lungs. Though a leukocyte filter (LF) is routinely incorporated into the EVLP circuit and believed to reduce circulating leukocytes from imparting cellular damage to the lung graft, its efficacy remains to be determined. We sought to characterize cellular and acellular perfusate leukocyte composition during EVLP and to investigate the efficacy of removing leukocytes with a LF.

Methods: Twelve pig lungs were perfused and ventilated ex-vivo in a normothermic state for 12 hours. Lungs (n=3) were allocated to 4 groups according to perfusate composition and the presence or absence of a LF in the circuit (acellular ± LF, cellular ± LF).

Results: Acceptable physiologic lung parameters were achieved during EVLP. Over 12 hours of EVLP, increased amounts of pro-inflammatory cytokines (TNF-α, IL-6) and leukocytes in the perfusate were observed despite the presence or absence of a LF. Analysis of cells washed off the LF at the end of EVLP demonstrates that it trapped leukocytes though was ineffective throughout perfusion as it became saturated over 12 hours.

Conclusion: Taken together we show that although leukocytes are demarginated from the lung and sequestered into the LF, the LF does not change the magnitude of inflammation caused during EVLP, as leukocyte activity remains prominent based on cytokine production. Therefore, a LF does not show benefit in EVLP. Methods to neutralize leukocytes pharmacologically rather than through trapping into a filter are required to minimize inflammation during prolonged EVLP.
HTN-BAS-1

ACUTE ELEVATION OF RENAL VENOUS PRESSURE INCREASES RENAL VASCULAR RESISTANCE VIA RENAL NERVES IN RATS

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*Authors contributed equally to this work.

Background: Systemic congestion leads to increased renal venous pressure (RVP), which could compromise renal hemodynamic and excretory function, in turn leading to fluid retention and deterioration of the heart failure. However, the underlying pathophysiological mechanisms are poorly understood. In the present study we tested the hypothesis that increases in RVP lead to increased renal vascular resistance (RVR) mediated by the renal nerves.

Methods: 20 male Lewis rats (300-400g) receiving a normal sodium diet were randomly assigned into 4 groups: intact time control (n=5) or increased RVP (n=5); renal denervation time control (n=5) or combined with increased RVP (n=5). Mean arterial pressure (MAP) and RVP were assessed using femoral artery and adrenal/spermatic vein catheters. GFR was measured by FITC insulin clearance. Left renal arterial blood flow (RBF) was directly measured by transit-time flow probe. To increase RVP, the left renal vein was partial occluded for 120 min. For renal denervation (RD), the renal nerves were stripped and painted with phenol to destroy remaining fibers bilaterally.

Results: Elevation of RVP from 0.9±1.0 to 11.5±1.8 mmHg (n=10) did not alter MAP compared to time control in intact (93.8±4.0 mmHg vs 94.2±3.1 mmHg) or RD (81.0±3.9 mmHg vs 78.8±3.9 mmHg) rats. RBF significantly decreased in the intact elevated RVP rats compared with time controls (p<0.05). RVR (calculated using the MAP-RVP difference) increased in intact rats compared to controls (14.7±0.5 vs 10.6±0.2 mmHg×min/ml, p<0.05). RD did not prevent a fall in RBF, but completely abolished the RVR increase. Acute modest increase in RVP did not appear to impact GFR.

Conclusion: Acute elevated RVP induces an immediate reduction in RBF followed by a steady increase in RVR mediated by renal nerves. This could imply that in congested states like heart failure, renal function is compromised by activation of the renal sympathetic nerves in response to elevated renal venous pressure.
HTN-BAS-2
TREATMENT OF HYPERTENSION BY RESVERATROL-ENHANCED FECAL TRANSPLANT

Suresh Baiwa, Nirmal Parajuli, Nobutoshi Matsumura, Jason Dyck

Background: Resveratrol is a bioactive phenol found in some plant-based food sources and has been used as a nutraceutical for the treatment of hypertension. We have recently shown that resveratrol ingestion induces taxonomic and functional changes of the gut microbiota and others have demonstrated that these changes in the gut microbiota are associated with lowering blood pressure in rats. Therefore, we hypothesized that fecal microbial transfer (FMT) from healthy resveratrol-fed donor mice would be sufficient to treat hypertension in mice.

Methods: 8-week old C57BL/6 mice were subcutaneously implanted with Alzet micro-osmotic pump to deliver saline or angiotensin (Ang) II (1.4mg/kg/day) for 2 weeks. These mice also received 3 FMTs over a one week period from feces from either healthy control chow fed or healthy resveratrol fed donor mice. Recipient mice were subjected to serial blood pressure measurement by tail-cuff pre and post-implant of micro-osmotic pumps of Ang II. At the end of the experiment, echocardiography was performed to assess heart function and mice were then euthanized for tissue collection.

Results: After 2 weeks, Ang II-treated mice that underwent FMT from chow fed diet (Ang II + Chow FMT) had significant elevated systolic blood pressure (SBP) compared with saline control (Saline + Chow FMT) (p<0.05). However, Ang II treated mice that received FMT from resveratrol fed donor mice (Ang II + Resv FMT) displayed a significant reduction in blood pressure compared to Ang II + Chow FMT group (p<0.05). In addition, heart weight to tibia length ratios were also significantly decreased in the Ang II + Resv FMT mice compared to the Ang II + Chow FMT group (p<0.05).

Conclusion: Our results show that SBP is increased by Ang II and this effect is prevented by FMT from healthy resveratrol-fed donor mice. Thus, our data suggest that resveratrol-induced alterations in the gut microbiota are sufficient to lower SBP mice, and that these changes may be an important mechanism by which resveratrol mediates its beneficial anti-hypertensive effects. Further tissue and gut microbiome analysis is required to understand the underlying mechanisms contributing to this novel regulatory pathway.
DIFFERENTIAL EFFECT OF 19,20-EPOXYDOCOSAPENTANOIC ACID (EDP) IN H9C2 CELLS GROWN IN HIGH OR LOW GLUCOSE CONDITIONS

Tomoko Endo, Victor Samokhvalov, K. Lockhart Jamieson, 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 low and high glucose concentrations toward 19,20-EDP-mediated effects in both normoxic and hypoxia-reoxygenation conditions in H9c2 cells.

Methods: H9c2 cells were cultured in DMEM containing either low (5.5mM) or high (25mM) glucose concentrations and supplemented with 10% fatal bovine serum (FBS), 1% penicillin and streptomycin at 37°C (5% CO2/65% N2). Cells were treated with 0 or 1µM 19,20-EDP and subjected to 30h normoxic or 24h hypoxic and 6h reoxygenation (H/R). Cellular viability was assessed by the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cell membrane integrity was determined using a fluorogenic peptide substrate (bis-AAF-R110, Promega), which cannot cross the intact membranes of viable cells, therefore reflects non-viable cells. Proteasomal activity was measured using an assay kit based on the detection of 7-amino-4-methylcoumarin (AMC) fluorescence after cleavage of the peptide LLVY-AMC. Cell lysates were assessed for caspase-3/7 activity using a profluorogenic peptide (rhodamine 110, bis-(N-CBZL-aspartyl-L-glutamyl-L-valyl-L-aspartic acid amide; Z-DEVD-R110, Promega).

Results: Under normoxic conditions H9c2 cells cultured in high glucose and treated with 19,20-EDP demonstrated significant loss in cell membrane integrity, decreased MTT reduction, increased proteasomal and caspase activity as well as decreased ATP production. The effects caused by 19,20-EDP were worsened following H/R treatment in high glucose conditions. In contrast, H9c2 cells cultured in low glucose conditions and treated with 19,20-EDP demonstrated increased MTT reduction and ATP production. Following H/R treatment, 19,20-EDP preserved cellular membrane integrity and viability as well prevented proteasomal and caspase activation while increasing 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. While in low glucose conditions, reflecting more oxidative phosphorylation, 19,20-EDP protected H9c2 cells.
IHD-BAS-2

CARDIOVASCULAR SUSCEPTIBILITY TO ISCHEMIC MYOCARDIAL INJURY IN MALE AND FEMALE RAT OFFSPRING BORN GROWTH RESTRICTED

Amin Shah, Nobutoshi Matsumura, Anita Quon, Jude S. Morton, Jason R.B. Dyck, Sandra T. Davidge

**Background:** Cardiovascular disease (CVD) is one of the leading causes of mortality in the world. It is now recognized that populations who suffer intrauterine growth restriction (IUGR), one of the most common consequences of complicated pregnancies, are more susceptible to develop CVD in later life. A consequence of CVD can be myocardial infarction (MI) and treatment for acute MI involves reperfusion, which is critical to saving lives but also results in cardiac injury. Using ex vivo techniques, our laboratory has previously shown that IUGR rat offspring had decreased cardiac tolerance to ischemia/reperfusion injury in adult life. However, the cardiac susceptibility of IUGR offspring following in vivo MI is not known. Therefore, we tested the hypothesis that adult male and female IUGR rat offspring are more susceptible to develop cardiac dysfunction following MI.

**Methods:** Male and female, control or IUGR rat offspring (created by exposing pregnant dams to hypoxia, 11.0±0.5% O2, for the last third of pregnancy) were randomly assigned to undergo sham or MI surgery at the age of 12 weeks. Thus the experimental groups consisted of: Control-sham, Control-MI, IUGR-sham, and IUGR-MI. One week after MI surgery, echocardiography was performed to assess cardiac morphometry, systolic function and diastolic function. Infarct size was measured using histology.

**Results:** Anterior LV wall thickness was decreased whereas LV internal diameter during diastole was significantly increased in both control-MI and IUGR-MI groups independent of sex or IUGR; indicating wall thinning and LV dilatation due to MI. Ejection fraction and fractional shortening were significantly decreased in both control-MI and IUGR-MI groups in male and female offspring. The Tei index was significantly increased in both control-MI and IUGR-MI male groups. Interestingly, E/E’ ratio, an index of LV filling pressure, was significantly increased in male but not female IUGR MI group (IUGR-Sham vs IUGR-MI: 19.84 ± 2.13 vs 35.21 ± 3.66, P<0.01). There was an overall effect of sex and IUGR in infarct size with male offspring having larger infarct size compared to female offspring.

**Conclusion:** MI was shown to alter LV wall morphometry leading to LV dilatation in both sexes. MI impaired systolic function independent of IUGR or sex. However, male IUGR offspring had greater infarct size and were more susceptible to develop diastolic dysfunction following MI. These studies indicate a susceptibility of the male IUGR population to develop heart failure involving diastolic dysfunction due to MI.
IHD-BAS-3

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

K. Lockhart Jamieson, Victor Samokhvalov, Maria Akhonkh, Xiuhua Wang, Zamaneh Kassiri, John M. Seubert

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

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

**Results:** Hearts from tAUCB-treated mice showed preserved ejection fraction and percent fractional area change compared to WT counterparts. However, no preservation of cardiac function was observed in sEH KO groups. All post-MI groups demonstrated a clear infarct. Mitochondrial functions were better preserved in both isolated mitochondria and cardiac fibers following myocardial infarction in hearts from tAUCB-treated and sEH KO mice based on higher respiratory control ratios compared to WT controls. tAUCB treatment increased post-MI enzymatic activity of complex I, II and IV. While there was no difference in post-MI groups, ATP levels were higher in the sham tAUCB and sEH KO groups compared to WT controls.

**Conclusion:** Our data suggest that while genetic deletion of sEH showed minor protective effects post-MI, pharmacological inhibition of sEH resulted in sustained mitochondrial bioenergetic efficiency and improved cardiac function.
IHD-BAS-4

PI3Kβ HAS DISTINCT ROLES IN ENDOTHELIAL CELLS AND CARDIOMYOCYTES IN RESPONSE TO MYOCARDIAL INFARCTION

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

Background: The cardiomyocyte-endothelial cell crosstalk plays an important role in myocardial infarction (MI). However the function of PI3Kβ, which is an isoform of class IA PI3K involved in the activation of pro-survival Akt pathway, in the heart is unknown. We test the function of PI3Kβ in endothelial cells and cardiomyocytes following MI in order to unveil the therapeutic potential of targeting PI3Kβ.

Methods: Mice with kinase-dead p110β (the catalytic subunit of PI3Kβ) expressed specifically in cardiomyocyte (p110βCre) or endothelial cell (p110βMer) were generated, and littermates (p110βFlx) were used as control. Intraperitoneal injection with tamoxifen was given to 9/10-week-old p110βMer mice to activate endothelial-specific gene deletion. Sham-operation or MI-surgery on 12-week-old mice and echocardiography after 7 days were performed in a blinded fashion. Mortality data were collected. TTC, CD31, and WGA staining were performed to test the infarct size, vascular density, and cardiomyocyte size on 7-day post-operated mice. Signaling pathways were assessed by Western blot.

Results: Successful deletion of specific p110β was confirmed by PCR. In sham groups, three genotypes showed comparable data on survival rate, cardiac function, vascular density, and cardiomyocyte size. However, on 7-day post-MI groups, p110βMer showed improved systolic function compared to p110βFlx, while p110βCre had deteriorated systolic function along with greater hypertrophy and lower vascular density in the non-infarct area. 7-day post-MI p110βMer hearts showed smaller infarct size. Moreover, higher vascular densities in peri-infarct and infarct areas of p110βMer group were observed, while cardiomyocyte size was similar. Despite similar protein levels of p110β and pAkt on sham-operated group, an increase of pAkt and pErk1/2 protein levels were present on 7-day post-MI hearts in p110βMer group. On p110βCre group, even though down-regulation of p110β protein level was seen on sham group, the protein levels of pAkt and pErk1/2 were unaltered on 7-day post-MI hearts compared to control group.

Conclusion: Protection from MI in p110βMer hearts might be due to an over-activation of PI3Kα regulated by feedback mechanism in the endothelial cells, up-regulating the angiogenic PI3K/Akt pathway. On the other hand, cardiomyocyte PI3Kβ is important in maintaining cardiac function after MI, probably via mechanisms independently of pAkt level.
IHD-BAS-5

DECELLULARIZED VENTRICULAR MATRIX AS A MODEL FOR STUDYING HUMAN MESENCHYMAL CELL PHENOTYPES

Alison Müller, Yilun Wu, Alois Haromy, Darren Freed

**Background:** As a result of pioneering research unveiling the influence of extracellular environment in determining stem/progenitor cell differentiation, a myriad of cellular scaffolds have been developed in order to optimize the delivery of these cells in a diseased environment as a technique to improve their efficacy in stem cell therapy. Although a variety of scaffolds are being studied in different contexts, the most physiologically relevant ones are those which most closely resemble the environment to be treated. Our lab has a keen interest in cardiovascular disease and we have recently optimized a technique that decellularizes and reseeds isolated sections of healthy porcine ventricular tissue with primary human atrial cells.

**Methods:** Porcine ventricular tissue was sliced between 100-200 μm and subject to a multi-step, multi-reagent washing process over a period of four days in order to decellularize the tissue. After decellularization, tissue slices were co-incubated with isolated primary human atrial fibroblasts (hAFs) or human c-kit(+) cardiac progenitor cells (hCCs). Cells were isolated from the atrial appendage of patients undergoing open heart surgery by mincing followed by collagenase digestion and subsequent isolation of hCCs was performed using a c-kit(+) magnetic bead isolation procedure. HAFs and hCCs were incubated separately on sections of decellularized porcine ventricular ECM over a period of 24 hours and then visualized using immunofluorescence. Successful seeding of cells was also evaluated by western blot detection of β-tubulin, a cytoskeletal marker.

**Results:** Collagen-1, fibronectin, and versican antibodies were used to image the ECM structure and DAPI was used to identify cells embedded in the recellularized matrix. Our technique was successful in reseeding decellularized porcine ventricular extracellular matrix determined by the presence of β-tubulin in recellularized tissue sections compared decellularized tissue sections. DAPI was not detected in decellularized tissue but was seen in recellularized tissue.

**Conclusion:** Our technique was successful in reseeding decellularized porcine ventricular extracellular matrix and can be extrapolated to detect other proteins in these tissues without having to reseed an entire decellularized heart. This 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.
ANGIOSTATIN DEMONSTRATES DIFFERENTIAL HYPOXIC-DEPENDENT ANTI-ANGIOGENIC MECHANISMS ON CARDIAC ENDOTHELIAL CELLS DERIVED FROM NON-VS TYPE II DIABETES

Natasha Govindasamy, Paul Jurasz

Background: Angiostatin is an endogenous platelet-generated anti-angiogenic mediator. Under hypoxic conditions, angiostatin inhibits endothelial cell (EC) matrix metalloproteinase (MMP)-2 and -14 expression and MMP-dependent EC migration, an early stage of angiogenesis. In addition, angiostatin may contribute to endothelial dysfunction as it inhibits endothelial nitric oxide synthase (eNOS) expression, thus potentially contributing to an unsuitable microenvironment for neovascularization. As reduced eNOS expression and NO biosynthesis has been reported for endothelial cells of Type II diabetics (T2D), and NO has been demonstrated to protect endothelial cells from both apoptosis and necrosis, our objective was to compare angiostatin’s anti-angiogenic effects on ECs derived from non- vs T2-diabetics. We hypothesized that during hypoxia angiostatin will decrease the expression of angiogenesis signaling and mediating proteins eNOS and MMP-2 within ECs derived from non-diabetic individuals, but that due to already reduced NO-mediated survival signaling it will induce death of T2D-derived ECs.

Methods: Human cardiac-derived microvascular ECs (HMVEC-C) from non-diabetics and T2-diabetics (dHMVEC-C) were cultured under standard conditions, and MMP-2 and eNOS levels were measured by immunoblot. HMVEC-C were treated with angiostatin (600 nM) or phosphate-buffered saline (PBS) and incubated under hypoxia (48 hrs. 5% CO2, balance N2), and MMP-2 and eNOS levels were determined by immunoblot. HMVEC-C and dHMVEC-C were treated with angiostatin (600 nM) under hypoxic conditions and apoptosis and necrosis was measured via flow cytometry. Transgenic eNOS-GFP mice were treated with angiostatin (30 μg) or PBS and underwent femoral artery ligation. Blood flow was measured by laser Doppler scanner.

Results: dHMVEC-C demonstrated lower MMP-2 expression compared to HMVEC-C (62±16% reduction n=3). Early passage (p5) dHMVEC-C also expressed less Enos than non-diabetic HMVEC-C, but this difference was lost with subsequent passages. Angiostatin caused attenuation of MMP-2 (38±9% reduction) and eNOS (62±18% reduction) expression in hypoxic non-diabetic HMVEC-C vs. PBS control. Angiostatin did not induce apoptosis or necrosis of hypoxic non-diabetic HMVEC-C. However, it did induce necrosis of hypoxic dHMVEC-C (6.98±2.1% vs control 3.03±0.3%). A single injection of angiostatin reduced the recovery in blood flow to the ischemic limb on day 14 (30±0.08% reduction). Further HLI experiments in a T2D model are required.

Conclusion: Preliminary data suggests that during hypoxia angiostatin inhibits expression of angiogenesis mediating proteins by non-diabetic ECs; whereas, it induces necrosis of T2D ECs. This induction of necrosis may be due to loss of NO-mediated survival signaling in T2D ECs. Finally, angiostatin neutralization may be an important potential treatment strategy to promote angiogenesis, particularly in T2D.
MULTIPLE MODELS OF PI3Kα DELETION IN THE HEART SHOW ISCHEMIA REPERFUSION PROTECTION WITH MAINTAINED MITOCHONDRIAL AND CELLULAR INTEGRITY

Brent McLean, Pavel Zhabyeyev, Alois Haromy, Bart Vanhaesebroeck, Evangelos Michelakis, Gavin Oudit

Background: The PI3K signaling axis has been identified as a mechanism for cardioprotection in ischemia/reperfusion (IR) injury. Paradoxically, PI3Kα dominant negative (PI3KαDN), a transgenic model for reduced PI3Kα in the heart, has enhanced recovery from IR injury. Our aim is to elucidate both the cell signaling and cellular physiology that cause PI3KαDN hearts to be resistant to IR damage, and see if these effects are also seen in an inducible PI3Kα knockout and pharmacological inhibition model. Down-stream activation of Akt and ERK1/2 are potential mechanisms of the PI3KαDN phenotype through protective effects on mitochondria. Current paradigms of IR induced cell death focus on mitochondrial protection as well as necrosis induction and cell membrane rupture. Using PI3KαDN as a model where cell death is reduced, we hope to identify cellular mechanisms that could be therapeutic targets to reduce cardiomyocyte death in IR injury.

Methods: Genetic mouse models include PI3KαDN and PI3Kαfl/fl Cre (40 mg/kg/day*2 days tamoxifen (TAM) P.O. 10-14 days before perfusion) and control littermates. Hearts from mice 12-14 weeks old are retrograde perfused using a Langendorff apparatus for 30 minute baseline, followed by 30 or 60 minutes of no-flow ischemia and 40 minutes of reperfusion with pressure recorded. Effluent is saved for assessment of protein content as an indicator of cell membrane rupture. The Akt inhibitor MK2206 (1 µM) and the MEK1/2 (kinase for ERK1/2) inhibitor MEK-162 (100 nM) and PI3Kα inhibitor BYL-719 (1 µM) are included for the entire perfusion in select groups. For live tissue imaging of cell death and mitochondrial membrane potential (ΔΨ), TMRE (100 nM) and Hoechst (500 nM) are added at reperfusion for 30 minutes with Sytox Green (1 µM) included for the last 10 minutes, followed by a 10 minute washout of all fluorophores before imaging by fluorescent confocal microscope. Molecular investigation includes Western blots looking at regulators of necrosis, apoptosis and the mitochondrial permeability transition pore.

Results: Inhibition of Akt and MEK1/2 failed to attenuate IR protection of PI3KαDN. PI3KαDN hearts had reduced protein release in reperfusion effluent. PI3Kαfl/fl Cre+TAM caused IR protection with both 30 and 60 min ischemia, similar to PI3KαDN. Perfusion of wildtype hearts with BYL-719 caused significantly improved IR recovery. PI3KαDN and PI3Kαfl/fl Cre+TAM live tissue imaging post IR showed maintained mitochondrial ΔΨ and fewer dead cells compared to control hearts. Necrosis regulators RIP1 and 3 protein levels were increased in non-perfused PI3KαDN hearts, but where lost in PI3KαDN and control hearts after IR.

Conclusion: Impaired PI3Kα causes robust IR protection in multiple models with reduced cell death and maintained mitochondrial ΔΨ. Cell death was primarily through necrosis and not apoptosis, but RIP signaling may not be involved. Characterization of regulators of mitochondrial ΔΨ is ongoing.
PROTEOLYTIC DEGRADATION OF CARDIAC TROPOSTIN I IN PATIENTS
WITH TYPE 1 AND TYPE 2 MYOCARDIAL INFARCTION

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Richard Schulz, Peter Hwang

Background: Myocardial infarction (MI) afflicts more than 70,000 Canadians each year. There are two common types: type 1 MI is caused by acute cholesterol plaque rupture and clot formation occluding a coronary artery, while type 2 MI is caused by an imbalance between cardiac blood supply and demand. It is vitally important to distinguish between the two because the treatments are drastically different. The gold standard for diagnosing MI is the serum cardiac troponin test. While it is known that cardiac troponin I (cTnI) is readily degraded in myocardial ischemia, it is unknown whether there is a difference in the degree of degradation in type 1 versus type 2 MI.

Methods: We collected blood samples from a total of 43 patients, some type 1 and some type 2. All type 1 patients had their diagnosis confirmed by angiography. The type 2 patients were determined to be such based on their clinical history. The blood samples were tested against a series of sandwich ELISA- (enzyme-linked immunosorbent assay)-based tests, using commercially available antibodies for cTnI. The capture antibody (19C7) recognizes a cTnI epitope from its well-structured core, while the detection antibodies target either the structured core (antibody 560), intrinsically disordered N-terminal region (M18), or C-terminal region (MF4).

Results: All three capture-detection antibody pairings were able to detect cTnI in patient samples. No obvious difference was noted between detection patterns for type 1 versus type 2 myocardial infarctions. However, at higher cTnI levels (which belonged exclusively to type 1 patients), the 19C7-560 antibody pairing started to yield higher readings than the 19C7-M18 and 19C7-MF4 antibody pairings, indicating increased proteolytic degradation and the N- and C-termini of cTnI as infarct size increased.

Conclusion: Preliminary analysis suggests that we cannot use proteolytic degradation to distinguish between type 1 and type 2 MI. However, in type I MI patients, there appears to be greater cTnI degradation in patients with bigger infarct sizes as indicated by higher cTnI levels. Further analysis will be done to determine clinically relevant patients-specific effects that could contribute to cTnI proteolysis, like the time before/after revascularization, time since symptom onset, and angiography results.
LIPMET-BAS-1

ADROPIN ENHANCEMENT OF CARDIAC INSULIN SENSITIVITY AND INHIBITION OF FATTY ACID OXIDATION ARE ASSOCIATED WITH IMPROVEMENT OF CARDIAC FUNCTION AND EFFICIENCY IN HEARTS FROM FASTED MICE

Tariq Altamimi, Arata Fukushima, Liyan Zhang, Su Gao, Abhishek Gupta, Gary D. Lopaschuk

Background: Impaired cardiac insulin signaling and high cardiac fatty acid oxidation rates are characteristics of diabetic cardiomyopathy. Potential roles for liver-derived metabolic factors in mediating cardiac energy homeostasis are underappreciated. Plasma levels of adropin, a liver secreted peptide, increase during feeding and decrease during fasting and diabetes. In skeletal muscle, adropin preferentially promotes glucose over fatty acid oxidation.

Methods: We therefore determined what effect adropin has on cardiac energy metabolism, insulin signaling and cardiac efficiency. C57Bl/6 mice were fasted to accentuate the differences in adropin plasma levels between animals injected 3 times over 24 hr with either vehicle or adropin (450 nmol/kg i.p.).

Results: Despite fasting-induced predominance of fatty acid oxidation measured in isolated working hearts, insulin inhibition of fatty acid oxidation was re-established in adropin-treated mice (from 1022±143 to 517±56 nmol. g dry wt⁻¹. min⁻¹, p <0.05) compared to vehicle-treated mice (from 757±104 to 818±103 nmol. g dry wt⁻¹. min⁻¹). Adropin-treated mice hearts showed higher cardiac work over the course of perfusion (p<0.05 vs. vehicle), which was accompanied by improved cardiac efficiency and enhanced phosphorylation of insulin signaling enzymes (tyrosine-IRS-1, AS160, p<0.05). Acute addition of adropin (2 nM) to isolated working hearts from non-fasting mice showed a robust stimulation of glucose oxidation compared to vehicle-treated hearts (3025±401 vs 1708±292 nmol. g dry wt⁻¹. min⁻¹, p<0.05, respectively) with a corresponding inhibition of palmitate oxidation (325±61 vs 731±160 nmol. g dry wt⁻¹. min⁻¹, p<0.05, respectively), even in the presence of insulin. Acute adropin addition to hearts also increased IRS-1 tyrosine-phosphorylation as well as Akt, and GSK3β phosphorylation (p<0.05), suggesting acute receptor- and/or post-translational modification-mediated mechanisms.

Conclusion: These results suggest adropin as a putative candidate for the treatment of diabetic cardiomyopathy.
LIPMET-BAS-2

INHIBITION OF MITOCHONDRIAL CALCIUM UPTAKE IN THE HEART DOES NOT COMPROMISE CARDIAC ENERGETICS OR FUNCTION DUE TO A PREFERENTIAL INCREASE IN FATTY ACID OXIDATION DURING INCREASED CARDIAC WORK

Tariq Altamimi, Arata Fukushima, Jeffery D. Molkentin, Gary D. Lopaschuk

Background: Cardiac mitochondrial uptake of calcium (Ca^{2+}), primarily mediated by the mitochondrial calcium uniporter (MCU), relays cytosolic calcium transients to mitochondrial metabolic machinery. Increasing cardiac workload by positive inotropes results in higher increases in glucose uptake and oxidation in comparison to relatively lower stimulation of fatty acids oxidation. This has been attributed to stimulation of intramitochondrial Ca^{2+} sensitive dehydrogenases including pyruvate dehydrogenase (PDH), the rate-limiting enzyme in glucose oxidation. However, it is not clear what effect increasing workload has on cardiac energetics and cardiac function if mitochondrial Ca^{2+} levels are decreased.

Methods: We therefore examined this in hearts from inducible cardio-specific deleted MCU (MCU-/-) mice. Hearts from MCU-/- and MCUfl/fl control mice were isolated and perfused as working hearts with 5 mM glucose, 0.8 mM palmitate, 3% albumin, either without insulin, with insulin (100 µU/ml) or with both insulin (100 µU/ml) and isoproterenol (10nM).

Results: Interestingly, MCU-/- hearts showed higher cardiac work over the course of perfusion (p<0.05 vs. MCUfl/fl) at comparable heart rates during all treatments. Unexpectedly, MCU-/- hearts were not energy-starved as they displayed basal rates of glucose and fatty acid oxidation comparable to controls, and even higher glucose oxidation in response to insulin (3027±213 vs. 2268±166 nmol.g dry wt^{-1}.min^{-1} in MCUfl/fl, p <0.05). In response to isoproterenol treatment, MCU-/- hearts showed a similar increase in glucose oxidation, compared to controls. However, palmitate oxidation increased to a greater extent in MCU-/- hearts compared to controls (793±60 vs. 558±55 nmol.g dry wt^{-1}.min^{-1}, p <0.05, respectively), resulting in a greater reliance on fatty acid oxidation for ATP production (40.1±1.9 % vs. 32.7±2.1% in MCUfl/fl ATP from palmitate oxidation, p <0.05). This high fatty oxidation supported the high energy demand under such increased workload and provided higher energy reserve as evident by higher acetyl-CoA/ CoA ratios (0.36±0.03 vs. 0.26±0.02 in MCUfl/fl, p<0.05). The rise in fatty acid oxidation correlated with lower levels of malonyl CoA, an endogenous fatty acid oxidation inhibitor, (4.50±0.29 vs. 8.66±0.98 nmol.g dry wt^{-1} in MCUfl/fl, p< 0.05), and to a stimulatory increase in acetylation of 3-hydroxyacyl CoA dehydrogenase, a key enzyme of the fatty acid β-oxidation pathway.

Conclusion: These results suggest that low mitochondrial Ca^{2+} does not compromise cardiac energetics due to a compensatory stimulation of fatty acid oxidation.
**Background:** As cardiovascular disease (CVD) represents the number one cause of death in type 2 diabetes (T2D) patients, there is a growing need to understand how T2D increases one’s risk for CVD. This includes diabetic cardiomyopathy, of which there are no approved therapies specifically for this condition. Previous studies have shown that myocardial glucose oxidation rates are markedly impaired during T2D due to reduced pyruvate dehydrogenase (PDH) activity, the rate-limiting enzyme for glucose oxidation. Furthermore, forkhead Box O1 (FoxO1) activity is enhanced in T2D and has been shown to increase expression of PDH kinase 4 (PDHK4), 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 directly controls PDHK4 transcription, and whether FoxO1 inhibition may be a novel approach to treat diabetic cardiomyopathy via preservation of PDH activity and glucose oxidation.

**Methods:** To examine the effect of FoxO1 modulation in PDH activity, C2C12 and H9c2 cells were differentiated into myotubes or myocytes, respectively, and treated with AS1842856 (1 µM; FoxO1 inhibitor) and/or Dexamethasone (10 µM; FoxO1 activator) for 24 hours in serum free media and Pdhk2 and PDHK4 mRNA expression, protein expression and PDH phosphorylation status were evaluated. In addition, C57BL/6J mice were fasted for either 20 hrs or 16 hrs followed by a 4 hr refeeding period, and animals sacrificed for extraction of the heart and muscles with the above mentioned mRNA and proteins evaluated. To examine the role of FoxO1 in regulation of the PDHK4 promoter, luciferase assays were performed in H9c2 cells transfected with a PDHK4 promoter-luciferase construct along with FoxO1 wild type (WT) or FoxO1-ADA (active form) or FoxO1-D256 (dominant negative) constructs.

**Results:** FoxO1 inhibition in C2C12 myotubes significantly decreased Pdhk2 and PDHK4 mRNA (~50%) and PDHK4 protein expression, which correlated with a significant decrease in PDH phosphorylation. Likewise, similar observations were seen in H9c2 ventricular myocytes. Dexamethasone induced PDHK4 mRNA in both C2C12 myotubes and H9c2 myocytes, which was markedly attenuated via pretreatment with AS1842856, and these findings translated to the appropriate changes in PDHK4 protein expression and PDH phosphorylation. As fasting is known to activate FoxO1, 20 hrs of fasting in mice leads to a significant decrease (~60%) in PDHK4 mRNA expression in soleus muscle compared to mice fasted for 16 hrs followed by a 4 hr refeed. The decrease in PDHK4 mRNA level was further corroborated by a decrease in soleus muscle PDH phosphorylation. Furthermore, luciferase activity assays showed significant upregulation of PDHK4 promoter activity by FoxO1-ADA and downregulation by FoxO1-D256 when compared to FoxO1 WT in H9c2 myocytes.

**Conclusion:** Our results suggest that FoxO1 controls PDHK4 transcription in the heart, and that it may regulate cardiac PDH activity and glucose oxidation. We are currently eliminating both FoxO1 and PDH specifically in the heart to delineate their roles in the pathogenesis of diabetic cardiomyopathy.
LIPMET-BAS-4

APPLICATION OF A NOVEL ANTI-PROTEOGLYCAN ANTIBODY TO INHIBIT ACUTE ARTERIAL RETENTION OF REMNANT LIPOPROTEINS IN A RAT MODEL OF INSULIN RESISTANCE

Yosdel, Soto, Rabban Mangat, Ana Maria Vazquez, Spencer Proctor

Background: The response-to-retention hypothesis suggests proteoglycan-lipoprotein interaction is the initiating step in atherosclerosis. Diabetic-dyslipidemia is associated with increased circulating remnant lipoproteins as well as increased arterial atherogenic proteoglycans. chP3R99 is a monoclonal antibody that recognizes glycosaminoglycan (GAG) chains of many proteoglycans and can interfere with GAG-lipoprotein binding. The direct effect of chP3R99 antibody on remnant-glycosaminoglycan interaction is not known.

The aim of this study was to assess the direct role of arterial glycosaminoglycans in the retention of apoB lipoproteins ex-vivo using antibodies against glycosaminoglycans in a rodent model of insulin resistance and CVD.

Methods: Cy5 labeled remnants (apoB48) were prepared via rabbit hepatectomy procedure. Control and insulin resistant carotid vessels were perfused ex-vivo with or without the chP3R99 antibody (125ug/mL, 20 minutes) followed by perfusion with Cy5-remnants (150ug/mL) with or without Cy3-LDL (150ug/mL) for 20 minutes. Retention of lipoproteins was evaluated using confocal microscopy.

Results: There was increased arterial retention of both remnants (3.6 fold more apoB48) and LDL (2.8 fold more apoB100) in carotid vessels from insulin resistant rats relative to control. Vessels that were previously perfused with ch3R99 antibody had substantially reduced lipoprotein binding. Antibody pre-perfusion resulted in decreased retention of remnants (-31%) and LDL (-59%) associated arterial cholesterol. Data suggests that the efficacy of the antibody to interfere with apoB particle attachment maybe lower for remnants (apoB48) relative to LDL (apoB100).

Conclusion: Remnants show preferential arterial accumulation compared to LDL during insulin resistance. Novel anti-proteoglycan antibodies provide an innovative approach for targeting retention of atherogenic apoB lipoproteins- potentially with differing affinity.
LIPMET-BAS-5

ANDROGENS MODULATE PLASMA AND INTESTINAL TRIGLYCERIDE AND CHOLESTEROL METABOLISM IN A PCOS-PRONE RODENT MODEL.


Background: In polycystic ovary syndrome (PCOS) a high plasma level of testosterone (T) has been correlated with an adverse plasma lipid profile and exacerbated CVD risk. At present we do not know the physiological or mechanistic pathways of how androgens regulate lipid metabolism under control and PCOS conditions. Previous studies from our laboratory have shown that flutamide, an androgen receptor (AR) inhibitor, reduces plasma concentration of triglycerides (TG) and apoB-lipoproteins, and intestinal secretion of TG. The aim of this study was to determine the direct and acute effects of testosterone and dihydrotestosterone (DHT) on lipid metabolism in control and PCOS-prone rodents.

Methods: Control and PCOS-MetS rodents were administered vehicle, testosterone propionate (T) or DHT (non-aromatizeable) for 7 days. Following treatment animals underwent a mesenteric lymphatic cannulation procedure to isolate intestinal chylomicrons and measure lipid absorption. Plasma and intestinal lymph was analyzed for lipids and apoB48-chylomicrons.

Results: T and DHT treatment increased plasma free T and reduced SHBG concentrations in control and PCOS-prone animals. Plasma LDL-C was increased with androgen treatment in both groups, with no effect on other plasma lipids. Intestinal TG and absorption of TG and cholesterol were upregulated in T and DHT treated PCOS-prone animals only, whereas DHT reduced intestinal apoB48 secretion in both control and PCOS-prone animals. These differential effects of T and DHT were associated with changes in lipidogenic genes (SREBP-2, ACC, MTP) and steroidogenic genes (AR, ER and SRDA51).

Conclusion: These results show androgens upregulate intestinal lipidogenic pathways in the synthesis and absorption of lipids, and differentially affect chylomicron secretion in PCOS-prone conditions. The significance of these findings is androgens may cause or exacerbate lipid and lipoprotein metabolism in PCOS. Further studies are exploring the androgen mediated-lipogenic pathways to determine specific targets and effective treatments to improve lipid metabolism in PCOS.
Background: Phosphatidylcholine (PC) is an integral membrane component in all mammalian cells. Phosphatidylethanolamine N-methyl transferase (PEMT) is an enzyme that is almost exclusively expressed in the liver and contributes ~30% of total hepatic PC synthesis. A major role for hepatic PC is surface coating of lipoprotein particles. Our lab has generated PEMT-/- mice and discovered that, on a high fat diet, they are strikingly protected from the development of diet induced obesity and insulin resistance. In addition, PEMT-/- / Ldlr-/- and PEMT+/+ / Ldlr-/- mice were developed and fed a high fat/high cholesterol diet. In PEMT deficient mice, very low density lipoprotein (VLDL) PC content was significantly lowered. These mice had decreased VLDL secretion but increased clearance, concomitant with the development of an atherosclerosis resistant phenotype. We suspect that due to decreased circulating VLDL, LDL-PC delivered to various tissues – including intestine – may be decreased. PEMT-/- mice have lower postprandial plasma triglyceride (TG) content which may be due to impaired chylomicron secretion.

Methods: Both PEMT-/- and PEMT+/+ mice were fed a chow diet until 10 weeks of age. Fasted mice were administered an olive oil bolus containing [3H]-oleic acid by oral gavage. Plasma and tissues were collected at 0.5, 1, 2, 4, and 8 hours post gavage. Tissue and lipid-specific location of radiolabel was determined via thin-layer chromatography separation and subsequent scintillation counting. Triglyceride, PC, and phosphatidylethanolamine were quantitated for determination of specific radioactivity.

Results: At 2 hours, PEMT-/- mice had more radioactivity in TG in the jejunum but this was ameliorated by 4 hours. Plasma TG remained lower in PEMT-/- mice compared to PEMT+/+ mice throughout the time course. Counts in plasma free fatty acids and white adipose TG were higher in PEMT -/- mice up to, respectively, 1 hour and 0.5 hours. Liver TG counts trended to be higher in PEMT -/- mice but this effect was gone by 4 hours.

Conclusion: PEMT-/- mice have delayed chylomicron secretion from the intestine. Chylomicrons either in, or derived from, PEMT-/- mice are handled differently post secretion than their PEMT+/+ counterparts. The role of peripheral tissue and chylomicron composition remains unclear. TG is more rapidly taken up by white adipose tissue, hydrolyzed and resecreted as free fatty acids to be transported to the liver. Increased plasma chylomicron content is a known risk factor for atherosclerotic development. PEMT -/- mice have lower postprandial plasma TG and are thus protected against or, less susceptible to, atherosclerosis related cardiovascular events.
TISSUE INHIBITOR OF METALLOPROTEINASE 4 (TIMP4) REGULATES ENERGY METABOLISM

Siva Sankara Vara Prasad Sakamuri, Wesam Bahitham, Abhijit Takawale, Subhash Das, Russell Watts, Gavin Y. Oudit, Richard Lehner, Zamaneh Kassiri

**Background:** Obesity and its associated comorbidities are important risk factors for the development type II diabetes and cardiovascular diseases. Tissue inhibitor of metalloproteases (TIMPs) are endogenous inhibitors of matrix metalloproteinases (MMPs) and regulate extracellular matrix (ECM) turnover of various organs including the adipose tissue. TIMP1, 2 and 3 have been shown to differentially affect the obesity outcome. TIMP4 is highly expressed in adipose tissue, and its levels are further elevated following high fat diet, but its role in fat metabolism under normal and obese conditions is not known.

**Methods:** Eight weeks old wild-type (WT) and TIMP4 knock-out (TIMP4KO) mice were divided into two groups each, one group received chow-diet (10% calories from fat) and the second group received high-fat-diet (HFD: 60% calories from fat) for twelve weeks. Food intake and body weights were monitored weekly, body composition (echo MRI), and basic metabolic rate (BMR) were measured after 10-12 weeks of each diet regimen. Plasma cholesterol profile (total, HDL and LDL), free fatty acids (FFA) and triglycerides (TG) were measured biochemically. Histology, morphometry, fibrosis and inflammation were assessed in the adipose tissue. Liver triglycerides (biochemical assay) and fat content (oil Red O staining), and fecal fat content and composition (thin layer chromatography) were measured in all groups. Protein and mRNA levels of candidate genes were assessed in the adipose tissue and liver.

**Results:** Chow-fed and HFD-fed TIMP4KO mice exhibited a higher food intake. TIMP4KO-HFD mice showed a reduced rate of weight gain, with lower body fat and visceral fat composition, and higher lean mass compared to WT-HFD mice. In addition, TIMP4-deficiency was associated with suppressed HFD-induced adipose tissue hypertrophy, fibrosis and inflammation (reduced macrophages infiltration and proinflammatory gene expression) in the adipose tissue. We further found that TIMP4KO-HFD mice have significantly reduced TG levels in the liver and skeletal muscle compared to the corresponding WT mice, did not show elevated plasma LDL-cholesterol and free fatty acid levels, and did not develop HFD-induced hyperinsulinemia. Chow-fed and HFD-fed TIMP4KO mice have reduced BMR, energy expenditure, but increased respiratory exchange ratio (RER) compared to the corresponding WT mice. Fecal fat analysis revealed higher TG and fatty acid excretion in TIMP4KO-chow fed compared to WT-chow fed mice, whereas only fatty acid levels were higher in TIMP4KO-HFD mice compared to WT-HFD mice.

**Conclusion:** TIMP4 gene deletion results in defective lipid digestion and absorption. This leads to suppressed body fat deposition, weight gain, and BMR with increased glucose utilization as the energy source. TIMP4-deficiency can protect against obesity and associated complications. Therefore, TIMP4 is an important regulator of energy metabolism under normal and obese conditions.
LIPMET-BAS-8
CARDIAC FATTY ACID UPTAKE IS NECESSARY FOR THE DEVELOPMENT OF PHYSIOLOGICAL HYPERTROPHY IN RESPONSE TO VOLUNTARY EXERCISE TRAINING IN MICE
Nikole J Byrne, Marc Mullen, Donna Beker, Jamie Boisvenue, Ian Robertson, Maria Febbraio, Jason RB Dyck

Background: Recent pre-clinical work has shown that limiting fatty acid entry into multiple organs such as the skeletal muscle and the liver is an effective approach to lessen obesity-induced insulin resistance. In addition, previous studies have shown that the preventing excessive fatty acid entry into the cardiomyocyte protects the heart from dysfunction induced by pressure overload in obese mice. While inhibiting fatty acid uptake in the presence of excess fatty acid availability may be beneficial in preventing cardiac dysfunction, the effect of reduced fatty acid uptake on physiological hypertrophy in the absence of chronic exposure to high circulating fatty acids is currently unknown. This is especially important as pharmacotherapies that limit multiple organ fatty acid uptake may have untoward effects on the heart.

Methods: To address this, we utilized a tamoxifen inducible cardiomyocyte-specific CD36 knockout (icCD36KO) mouse and genetically deleted CD36 (a major fatty acid transporter in most cells) in hearts of adult mice using tamoxifen administration. 18-20 week old control mice (CD36 flox/flox mice treated with tamoxifen) and icCD36KO mice were housed with or without ad lib access to a running wheel. Mice were subjected to echocardiography prior to and following 3 weeks of exercise training in order to assess changes in cardiac function (determined by %ejection fraction; %EF) and morphology.

Results: Control and icCD36KO did not differ in run time (4.05±0.50 vs. 4.02±0.43 hrs/d), distance run (6.31±1.34 vs. 6.46±1.22 km/d) or average speed (1.67±0.17 vs. 1.71±0.20 km/hr). No significant difference in systolic function was observed between control and icCD36KO mice at baseline (%EF; 60.5±1.38 vs. icCD36KO; 58.4±1.94); however icCD36KO mice displayed a modest increase in posterior wall thickness compared to control mice (0.70±0.02 mm vs. 0.75±0.02 mm, respectively; P<0.05). Following exercise training, control mice developed physiological hypertrophy, evidenced by increased posterior wall thickness (control run; 0.93±0.05 mm vs. control sedentary; 0.76±0.03 mm; p<0.05) and a 12.3% increased in wet heart weight (n=6-7; P<0.05). However, these same morphological changes observed in control mice were not statistically significant in icCD36KO mice in response to exercise training (n=5-6). Furthermore, control mice had significantly increased %EF following exercise training (control run; 69.9±3.1% vs. control sedentary; 61.2±2.2%; p<0.05), which was not observed in icCD36KO mice (icCD36KO run; 55.8±4.7% vs. icCD36KO sedentary; 61.0±4.8%).

Conclusion: These data suggest that limiting fatty acid uptake in the heart via CD36 ablation lessens exercise-induced physiological remodeling. Thus, the proposed use of CD36 inhibitors as a treatment for obesity-induced insulin resistance may have negative consequences in terms of preventing adaptive cardiac remodeling.
ALTERED PLASMA LIPID PROFILE, LIPOPROTEIN SECRETION AND CAPACITY TO TOLERATE A HIGH FAT DIET IN A MOUSE MODEL WITH REDUCED INTESTINAL PHOSPHATIDYLCHOLINE BIOSYNTHESIS

John P. Kennelly, Jelske van der Veen, Susanne Lingrell, Randy Nelson, Robin da Silva, Kelly-Ann Leonard, René L. Jacobs

Background: Phosphatidylcholine (PC) is the primary phospholipid in mammalian cell membranes, lipid droplets and plasma lipoproteins. PC is produced from dietary choline by the CDP-choline (Kennedy) pathway in all nucleated cells, and the enzyme CTP: phosphocholine Cytidyltransferase (CT) regulates flux through the pathway. CTα, the predominant isoform in most major tissues, is an important regulator of very-low density lipoprotein (VLDL) and high-density lipoprotein (HDL) metabolism in the liver. Furthermore, PC biosynthesis is important for maintaining the structural integrity of membranes and for facilitating the incorporation of fatty acids into lipid droplets to avoid cell toxicity. Therefore, CTα may play a role in intestinal dietary fat metabolism. To determine the functional importance of CTα and PC in regulating intestinal lipid and lipoprotein metabolism in vivo, we have generated intestinal-specific CTα deficient mice (iCTα -/-) mice using a tamoxifen-inducible Cre-Lox system.

Methods: iCTα -/- and floxed control mice were fed either a chow diet for two weeks or a 40% high fat diet for one week. Blood and intestinal tissue was collected for lipid, transcriptional and histological analysis. CTα enzyme activity was assessed by providing {3H} phosphocholine to intestinal homogenates and measuring production of {3H} CDP-choline. Chylomicron secretion was assessed by administering mice with an oral bolus of olive oil and measuring appearance of triglyceride in plasma at various time-points. Phospholipid levels were measured by TLC; and plasma glucose, cholesterol and triglycerides were measure with commercially available kits.

Results: CTα enzyme activity was absent in iCTα -/- mice, while control enterocytes had abundant enzyme activity. When maintained on a low fat, high carbohydrate rodent chow (4% fat, 76% CHO) for two weeks, iCTα -/- mice appeared healthy; had normal fasting plasma glucose and lipid levels; and had normal chylomicron secretion as assessed by a lipid tolerance test; compared to controls. However, when maintained on a high fat diet (40% fat, 35% CHO), iCTα -/- mice rapidly lost weight and became moribund, suggesting an inability to tolerate the fat content of the diet. Fasting plasma glucose, triglyceride and cholesterol levels were reduced in high fat fed iCTα -/- mice compared to controls. A lipid tolerance test of 5-day high fat diet-fed mice showed that iCTα deletion reduced chylomicron secretion rate as compared to controls with normal CTα activity. Furthermore, levels of triglyceride and cholesterol were lower in intestinal tissue of iCTα -/- mice compared to control levels.

Conclusion: These findings suggest CTα plays an important role in regulating intestinal lipid and lipoprotein metabolism during high fat feeding. Future studies will investigate the mechanisms behind altered lipid metabolism in iCTα -/- mice.
MALONYL CoA DECARBOXYLASE INHIBITION IMPROVES CARDIAC FUNCTION POST MYOCARDIAL INFARCTION

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Background: Alterations in cardiac energy metabolism following a myocardial infarction (MI) contribute to the development and severity of heart failure. The alterations in mitochondrial oxidative metabolism in the failing heart include a decrease in glucose and fatty acid oxidation, as well as an increase in cytosolic glycolysis, as the heart attempts to compensate for the decrease in mitochondrial energy production. Glycolysis is a much less efficient source of energy, and the increase of which can result in its uncoupling from glucose oxidation which, in turn, can increase proton production. One potential approach to enhancing cardiac efficiency in the post-MI heart is to improve the coupling between glycolysis and glucose oxidation by inhibiting fatty acid oxidation. We determined if inhibition of malonyl CoA decarboxylase (MCD), a key enzyme modulating cardiac fatty acid oxidation, could improve cardiac efficiency and decrease the severity of heart failure post-MI.

Methods: Sprague Dawley rats were subjected to a permanent left anterior descending coronary artery ligation (Cal), and a predictable heart failure developed over the next 7 weeks. An MCD inhibitor, CBM-3001106, was administered either chronically at a high dose (100mg/kg) or a low dose (50 mg/kg) over a 4-week period to a set of rats 3 weeks post-surgery, or acutely post-surgery to a separate set. Echocardiogram analysis was performed to measure cardiac function, and isolated working heart perfusions were performed to measure cardiac energy metabolism. Biochemical analysis was performed on tissues to measure protein expression and activity.

Results: Acute MCD inhibition significantly improved cardiac function in MI hearts, showing increased left ventricular ejection fraction (%EF) and stroke volume, and a decreased peak elastance compared to control groups. Chronic MCD inhibition significantly improved cardiac function post-MI, with improved %EF (53% ± 2% vs. 44% ± 2%, n=7-10, p<0.05), and cardiac efficiency (0.021 ± 0.001 vs. 0.014 ± 0.001 joules/µmol, n=7-10, p<0.05) seen in the MI + high dose group compared to the MI + Vehicle group. Chronic MCD inhibition decreased cardiac fatty acid oxidation rates, and decreased proton production rates from glycolysis uncoupled from glucose oxidation. Decreased endoplasmic reticulum stress, and increased protein expression of thioredoxin as well as mitochondrial superoxide dismutase activity was also seen with MCD inhibition in post-MI hearts.

Conclusion: Chronic MCD inhibition reverses cardiac dysfunction in rats with established heart failure by improving cardiac energy efficiency due to optimizing cardiac energy metabolism and enhancing anti-oxidative capacity in the failing hearts.
LIPMET-BAS-11

OBESITY FROM LEPTIN RECEPTOR DEFICIENCY PROVIDES RESISTANCE TO THE DEVELOPMENT OF PULMONARY HYPERTENSION FROM MONOCROTALINE

Vikram Gurtu, Adam Kinnaird, Spencer Proctor, Gopinath Sutendra, Evangelos Michelakis

Introduction: Pulmonary arterial hypertension (PAH) is a proliferative vascular disease characterized by mitochondrial suppression in the pulmonary artery and right ventricle (RV), but also other systemic tissues, similar to what is seen in metabolic syndrome and obesity. Some studies suggest that obesity may paradoxically be a protective factor in PAH, similar to what has been shown in congestive heart failure (i.e. the obesity paradox). As leptin receptor polymorphisms, hyperleptinemia, and leptin resistance are associated with obesity, we hypothesized that obese, leptin receptor deficient rats (JCR:LA-cp rats) would be protected from developing pharmacologically induced PAH by monocrotaline (MCT), a standard PAH model.

Methods: JCR:LA-cp rats were given intraperitoneal injections of MCT (n=6) vs. vehicle (n=6) and compared to lean JCR rats (n=6 MCT and n=6 vehicle). After three weeks, hemodynamics were assessed using echocardiography and right heart catheterizations with Millar catheters.

Results: Leptin receptor deficient rats were more obese than lean controls (weighing 528 ± 8g versus 343 ± 4g). In lean control rats (normal leptin receptor levels), MCT increased RV systolic pressure (RVSP) compared to vehicle (43.0 ± 3.5mmHg vs. 26.2 ± 0.7mmHg, p<0.01), and increased RV mass (221 ± 19mg vs. 161 ± 9mg). Furthermore, cardiac output was reduced in MCT lean rats compared to vehicle (120.8 ± 7.5µL/min vs. 84.2 ± 9.7µL/min, p<0.05). However in obese, leptin receptor deficient rats, MCT did not increase RVSP vs. vehicle (33.5 ± 4.1mmHg vs. 30.2 ± 1.3mmHg) or RV mass and cardiac output was unchanged.

Conclusion: Leptin receptor deficient rats are resistant to MCT induced PAH indicating that leptin downstream signaling may contribute to pulmonary vascular and RV remodeling. Impaired leptin signaling in obesity may explain the “obesity paradox” of PAH, revealing a novel pathway that could be therapeutically targeted in PAH.
LIPMET-BAS-12

C-MYC 1 IS REVERSIBLY INDUCED BY SUPPRESSION OF MITOCHONDRIAL FUNCTION AND MAY BE INVOLVED IN EMT

Aristeidis E. Boukouris, Adam Kinnaird, Roxane Paulin, Gopinath Sutendra, Sotirios Zervopoulos, Vikram Gurtu, Evangelos D. Michelakis

Background: Epithelial-to-mesenchymal transition (EMT) is implicated in cardiovascular development and disease, as well as cancer progression; but its molecular basis is incompletely understood. We speculated that metabolic signals, which have been shown to be altered during heart development and during myocardial and vascular disease, may be important for EMT. We hypothesized that primary mitochondrial inhibitors would induce EMT signaling.

Methods: We exposed epithelial cells to well-known inhibitors of mitochondrial function: Ethidium Bromide (EtBr; depletes mitochondrial DNA), Oligomycin (ATP synthase inhibitor), hypoxia (global inhibitors of mitochondrial function), Ciprofloxacin (an antibiotic with known anti-mitochondrial effects) or siRNA against sirtuin-3 (the main mitochondrial deacetylase, the absence of which globally suppresses mitochondrial function). We quantified mitochondrial function measuring respiration (Seahorse Analyzer) and measured morphological and molecular factors that have been shown to be important in EMT.

Results: Mitochondrial inhibitors predictably suppressed mitochondrial function in a dose-dependent manner and induced characteristic features of EMT, i.e. spindle-like cell morphology. c-Myc (a transcription factor important for metabolic regulation in myocardial and vascular cells, and a well-known driver of EMT in cancer) was also induced in an isoform-specific manner: a robust induction of c-Myc 1 was observed in cells treated with all of the tested mitochondrial inhibitors. However, c-Myc 2 was increased by EtBr but decreased by Ciprofloxacin and siRNA inhibition of SIRT3. Removal of mitochondrial inhibitors restored mitochondrial function and normalized the c-Myc 1/c-Myc 2 ratio in the same cells. In EtBr-treated cells, the levels of c-Myc 1 negatively correlated quantitatively with mitochondrial DNA levels and respiration. siRNA inhibition of both c-Myc 1 and 2 inhibited the expression of the EMT markers SNAIL and E-cadherin without changing the levels of the EMT marker ZEB1. When c-Myc2 (but not 1) was inhibited, ZEB1 expression was decreased.

Conclusion: We found that primary mitochondrial inhibition may cause EMT. We also found that primary metabolic suppression causes an induction of c-Myc 1, an isoform, that in contrast to c-Myc 2, little is known about its function (other than it is induced by lack of essential amino acids, a condition that is mimicked by primary mitochondrial inhibition). It appears that changes in the c-Myc 1/c-Myc 2 ratio in response to mitochondrial suppression, may be a part of a conserved molecular program to link metabolic stress with cell fate, including EMT, which may be explored therapeutically in cardiovascular disease and cancer.
LIPMET-BAS-13

DOES DIETARY CHOLINE SUPPLEMENTATION INCREASE ATHEROSCLEROSIS IN LDLR-/- MICE


Background: Choline is an essential nutrient that is required cell membranes, lipoprotein secretion and methyl-group metabolism. Recently, choline supplementation was shown to enhance atherosclerosis in ApoE-/- mice. This association was dependent on the conversion of choline to trimethylamine (TMA) by gut microbiota; TMA is oxidized to trimethylamine-oxide (TMAO) by the liver enzyme, flavin-containing monooxygenase-3. Furthermore, circulating choline, betaine (the oxidized form of choline) and TMAO have been associated with increased risk of CVD in numerous human trials. The aim of this study was to determine whether dietary choline or betaine promote atherosclerosis in low-density lipoprotein receptor knockout (Ldlr-/-) mice.

Methods: Ldlr-/- male mice (N=17), aged 8-10 weeks, were randomized to one of three dietary groups: control ((n=5) 0.1% choline wt/wt and 0% betaine wt/wt), choline supplemented ((n=6) with 1% choline wt/wt, 0% betaine wt/wt), or betaine supplemented ((n=6) 0.1% choline wt/wt, 0.9% betaine wt/wt). All diets contained high fat (40% of calories) and 0.5% of cholesterol. Animals were housed in colony cages in a temperature-controlled environment (22°C-25°C) with a 12 h light/dark cycle and had free access to food and water. After the 8-week dietary intervention, the animals were euthanized, and tissues and blood collected. Aortic atherosclerotic plaque area, plasma choline and lipid metabolites were quantified. Liver histology and lipids were analyzed.

Results: Dietary supplementation with choline or betaine did not alter weight gain, liver weight or gonadal WAT. Atherosclerotic plaque did not differ between the control and betaine supplemented group. To our surprise, choline supplementation reduced plaque development as compared to control diet fed animals. Despite having less atherosclerosis, choline-supplementation increased plasma TMAO levels as compared to control animals. No change was observed in plasma cholesterol, triglycerides, choline or betaine between dietary groups. Hepatic TG trended to be lower in the choline- and betaine-supplemented groups as compared to control animals.

Conclusion: The results of this pilot study were surprising. Choline-supplemented Ldlr-/- mice have reduced atherosclerotic lesion area despite an increase in plasma TMAO levels. Future work is required to understand the relationship between dietary choline and atherosclerosis in the Ldlr-/- mouse model.

VASD-BAS-1

ACTIVATORS OF K\textsubscript{Ca} CHANNELS ENHANCE ENDOTHELIUM-DEPENDENT MODULATION OF NERVE-EVOKED CONSTRICTION IN RAT MESENTERIC ARTERIES

Stephanie E. Lunn, Shaun Sandow, Tim V. Murphy, Ran Wei, Paul M. Kerr, Frances Plane

Background: The sympathetic nervous system and the vascular endothelium act in concert to regulate arterial diameter and thus blood flow and pressure. Vasoconstriction triggers a negative feedback response whereby activation of endothelial small (SK\textsubscript{Ca}) and intermediate (IK\textsubscript{Ca}) conductance calcium-activated potassium channels and/or release of endothelium-derived (NO), limit further reductions in vessel diameter. We hypothesize that small molecule activators of SK\textsubscript{Ca} and IK\textsubscript{Ca} may provide a novel means to enhance endothelial function in disease states. Thus, here we have investigated whether such drugs can enhance endothelial modulation of nerve-evoked vasoconstriction

Methods: Nerve-evoked vasoconstriction was measured as an increase in perfusion pressure in the rat perfused mesenteric bed.

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

Conclusion: These data indicate different functional roles SK\textsubscript{Ca} and IK\textsubscript{Ca} channels in endothelium-dependent modulation of nerve-evoked vasoconstriction of mesenteric arteries; SK\textsubscript{Ca} channels appear to be involved in NO-mediated attenuation of vasoconstriction whereas activation of IK\textsubscript{Ca} channels is linked to an NO-independent pathway. The ability of KC\textsubscript{a} channel activators to suppress nerve-evoked constriction supports the proposal that these channels may provide novel targets for drugs to overcome the endothelial dysfunction and increased sympathetic outflow associated with the development of hypertension.
HEART AND LUNG ENDOTHELIAL CELLS EXHIBIT HETEROGENEITY IN THEIR MECHANISM OF RESPONSE TO HYPOXIA WITH REGARD TO VON WILLEBRAND FACTOR EXPRESSION

Anahita Mojiri, Maria Areli Lorenzana Carrillo, Radya Yousef Abdulla, Maryam Nakhaei-Nejad, Consolato M. Sergi, Bernard Thebaud, William C. Aird, Nadia Jahroudi

Background: Von Willebrand factor (VWF) expression is highly endothelial specific, but also heterogeneous expressed in different vascular beds in vivo. We have previously demonstrated that in a mouse model of pulmonary hypertension induced by hypoxia VWF is upregulated in all major organs, but not kidney. Specifically in lung, pattern of VWF expression was altered from primarily large vessels in control to that of micro- as well as macro- vessels in hypoxic lung. Our objectives in the current studies were to explore the mechanisms that govern hypoxia-response of VWF in cardiac versus lung endothelial cells (ECs). We also aimed to determine the functional consequences of hypoxia-induced VWF in regard to thrombogenicity in different organs.

Methods: Cultured ECs of various organs were used to determine their response to hypoxia with regard to VWF expression. Adenoviral vectors containing various VWF regulatory regions fused to LacZ gene were generated to determine regulatory regions that mediate hypoxia responses of VWF in heart vs. lung ECs. Chromatin immunoprecipitation analysis and DNA methylation assessment were performed to determine alteration in transcription factors binding pattern, as well as epigenetic modification of VWF promoter in cardiac and lung ECs in response to hypoxia. siRNA against various VWF regulatory transacting factors were used to determine their role in hypoxia induction of VWF. Various organs of hypoxia-exposed and control mice were analyzed for the presence of platelet aggregates and thrombus formation.

Results: Differential hypoxia responses of VWF gene in mouse ECs of distinct organs in vivo were reflected in cultured human endothelial cells of corresponding organs. ECs of heart and lung employed distinct regions of VWF regulatory sequences for hypoxia response. Distinct patterns of transacting factors interaction with the VWF promoter in lung and heart EC in response to hypoxia were demonstrated. This included a reduction in binding of the repressor NF-IB to the VWF promoter in both cell types. However, in lung ECs YY1 participated in hypoxia-induction of VWF, but in cardiac ECs GATA6 and HIF participated in this process. Analysis of methylation pattern demonstrated that a CpG dinucleotide located at the proximity of repressor NF-IB binding site was hypermethylated in response to hypoxia specifically in cardiac EC. In mice, VWF upregulation in response to hypoxia was concomitant with presence of thrombi specifically in heart and lung.

Conclusion: Hypoxia induced VWF upregulation were associated with thrombus formation in microvessels of the heart and lung but not kidney. Although hypoxia induction of VWF occurs in ECs of heart and lung, distinct organ-specific molecular mechanisms are invoked to elicit this response in each cell type.
Background: Both apelin and angiotensin converting enzyme 2 (ACE2) pathways are cardiovascular protective by antagonizing angiotensin II action. However, the role of apelin in vascular pathology is unclear. In this study we examined the role of apelin in vascular diseases and the connection with the ACE2 axis.

Methods: WT and APLN⁻/⁻ mice were treated with Ang II (1.5 mg/kg/d for 4 weeks) by subcutaneous micro-osmotic pump. Aortic remodeling and functional properties were characterized, by gross histological assessment, multiple histological and immunofluorescent staining and echo ultrasound vasculography, as well as expression assessment for Apelin and ACE2 by Taqman and western blot assay. Acute vaso-tonic effects of Ang II in WT or APLN⁻/⁻ mesenteric arteries were studied by pressure myography together with the ACE2 expressional level study. Phenylephrine (PE) treatment group was included as a positive control, to address the potential involvement of hypertension in the aortic remodeling. We further used primary aortic smooth muscle cells (SMCs) from humans and from mice to rule out the involvement of blood pressure in our in vivo observations. Apelin expression in SMCs was manipulated by siRNA technique, which was followed by Ang II treatment, and subsequently apoptotic assessment by annexin V + PI double staining and flow cytometry as well as reactive oxygen species (ROS) assessment by DHE staining and NADPH Oxidase activity assay. Exogenous apelin was given to rescue Ang II-induced vascular remodeling in ApoE KO mice.

Results: Loss of apelin, with decreased ACE2 expression, potentiate Ang II effects leading to greater arteriolar constriction acutely ex vivo, and exacerbated hypertension and adverse aortic remodeling in vivo, as demonstrated by abdominal aortic rupture, fibrosis, apoptosis and aneurysm. Ang II treatment triggered upregulation of ACE2 in aorta as well as upregulation of apelin at the same time. Loss of apelin abolished the ACE2 upregulation in response to Ang II in the aorta. Apelin knockdown in human or mouse aortic SMCs leads to greater increase in apoptosis in response to Ang II treatment as well as greater increased ROS formation. Apelin supplementation rescued the fibrotic response in aorta induced by Ang II in WT and ApoE KO mice in vivo.

Conclusion: Apelin counteracts the detrimental effects of Ang II in the vasculature by upregulating ACE2. These results highlight a new synergistic mechanism in support of enhancing apelin and ACE2 action in treating cardiovascular diseases.
ENDOTHELIAL CELL HETEROGENEITY: CORRELATION BETWEEN VON WILLEBRAND FACTOR AND GATA TRANSCRIPTION FACTOR FAMILY EXPRESSION IN DISTINCT ORGANS

Areli Lorenzana-Carrillo, Anahita Mojiri, Nadia Jahroudi

Background: Endothelial cells (EC) of different organs exhibit heterogeneity in structure, function and gene expression. This also extends to the pattern in which the highly endothelial specific gene, von Willebrand Factor (VWF) is expressed. VWF is an adhesive protein, involved in regulation of hemostasis and thrombosis. It was previously demonstrated that nucleotides -487 to 247 of the VWF gene function as an endothelial-specific promoter that exhibits organ-specific activity. We hypothesised that pattern of expression of transcription factors that regulate the VWF promoter may contribute to the mechanism that governs organ-specific regulation of the VWF promoter. VWF promoter contains binding site for GATA family of transacting factors and mutation of this site was shown to abolish the VWF promoter activity in vitro and in vivo. Several members of GATA family, including GATA2, 3 and 6 were reported to interact with the VWF promoter. We tested the hypothesis that there may be organ-specific distribution of GATA family member which could contribute to organ-specific regulation of VWF

Methods: Immunofluorescence staining was used in various murine organs to mark the VWF and CD31 expressing EC. We also co-stained for transacting factor GATA family members GATA2, 3 and 6

Laser Capture Microdissection (LCM) was used to mark and dissect 1 to 10 cells of 3 sets of different cells of lung including; VWF expressing EC and cells that were not EC and did not expressed VWF. RT-PCR was used to analyse gene expression pattern in the dissected cells.

Results: Our IF and confocal microscopy demonstrated that ECs of distinct organs exhibit distinct patterns of GATA isoforms. Using IF and LCM we were able to positively identify, capture and isolate target cells. RT PCR analyses of isolated target cells demonstrated significant VWF expression in dissected EC, which was comparable to cultured EC.

Conclusion: These data suggest that we have an organ specific expression pattern of GATA transcription factors that may participate in organ-specific regulation of VWF transcription. The use of laser capture microdissection system will allow us to specifically detect the expression pattern of distinct regulatory factors that participate in regulation of the VWF gene in EC of distinct organs.
AGE-RELATED ALTERATIONS IN THE LEVEL AND EXPRESSION PATTERN OF PROTHROMBOTIC PROTEIN VON WILLEBRAND FACTOR (VWF)

Radya Abdualla, Anahita Mojiri, Areli Lorenzana-Carrillo, Nadia Jahroudi

**Background:** Von Willebrand Factor (VWF) is a multimeric adhesive glycoprotein that is exclusively expressed in endothelial cells (EC) and megakaryocytes. This procoagulant protein is involved in maintaining primary hemostasis and thrombus formation. However, there are pathological and physiological conditions that alter the circulating levels and pattern of VWF expression in vasculature. Unregulated increase in VWF levels may contribute to elevate the incidence of thrombosis. Since increased thrombogenicity is observed with aging, we explored whether aging is associated with alterations in levels and/or pattern of VWF expression.

**Methods:** We compared circulating VWF levels in the blood of young and aged mice and rats, using Elisa. Additionally, Immunofluorescent confocal microscopy as well as RT-PCR analyses were used to determine mRNA levels and the expression pattern of the VWF protein, combined with the endothelial marker CD31 and micro vessels marker (Isolectin-GS-IB4), in the brains, livers, hearts, kidneys and lungs of young and aged mice.

**Results:** With age VWF expression at mRNA levels were significantly increased in brains, lungs, and livers, but not in kidney and heart of aged mice compared to young. Also circulating VWF protein levels increased in blood of aged rats compared to young. Moreover, the endothelial staining intensity of VWF increased in micro and macro vessels of brains, lungs, and livers of aged compared to young mice.

**Conclusion:** With aging, VWF levels are increased in circulation. Furthermore, an altered VWF expression pattern, specifically increased expression in microvasculature of brain, lung, and liver, is observed. Overexpression of VWF in circulation and micro vessels of distinct organs as a result of aging may contribute to vascular diseases such as thrombosis.
**EFFECTS OF HUMAN PLATELETS ON LUNG CANCER STEM CELL INVASION**

MengJie Yan, Paul Jurasz

**Background:** The cancer stem cell theory of cancer origin suggests a small population of cancer cells has stem cell-like characteristics (CSCs) and is responsible for initiating new tumors following metastasis. Studies have shown that cancer cells activate platelets and that platelets contribute to metastasis, in part by stimulating cancer cell invasion. Stromal derived factor-1α (SDF-1α) secreted from activated platelets is known to mobilize stem and cancer stem cells via increased matrix metalloproteinase (MMP) expression. We hypothesize that activated platelets release SDF-1α which binds to its receptor CXCR4 on CSCs leading to increased MMP production, and thus preferentially induce CSC invasion.

**Methods:** A549 lung carcinoma CSCs were identified either as Hoechst 33342-negative side population (SP) and/or sorted using fluorescence activated cell sorting based on CD133 positivity. CSC invasion was compared to total A549 population invasion via modified Boyden Chamber assays in response to collagen-activated human platelet releasates and quantified by flow cytometry and confocal microscopy. MMP-2 and -9 levels are compared using gelatin zymography.

**Results:** Activated platelet releasates preferentially stimulated invasion by SP-identified CSCs (4.3±0.3% of total population A549 pre- vs. 7.6±0.7% post-invasion, P<0.05). The CXCR4 antagonist AMD3100 (10μM) failed to inhibit SP-invasion, but inhibited total A549 invasion (60.85±13.37x10³ total-population invasion without vs. 44.23±9.88x10³ with, P<0.05). Preliminary data suggest CD133-positive A549 cell invasion increased compared to CD133-negative cells in response to activated platelet releasates (40.50±10.36% CD133-negative vs. 60.25±9.73% CD133-positive, P=0.2). Further, CD133 staining demonstrated that the Hoechst negative SP is enriched with CD133-positive cells (1.4± 0.59% in total vs. 3.84±1.09% in A549 SP, P<0.05). CD133-positive cells have higher basal MMP-2 levels than CD133-negative cells (37.87±15.05 CD133-negative vs. 53.77±17.02 CD133-positive cells, P<0.05). Treatment with washed platelet for 24Hrs lessens the difference by increasing MMP-2 levels in CD133-negative cells (1.71±0.78 CD133-negative vs. 1.60±0.75 CD133-positive cells, P=0.39). MMP-9 levels remain similar in A549 cells before/after platelet treatment (Before: 1.65±1.17 CD133-negative vs. 2.25±1.58 CD133-positive cells, P=0.36; After: 1.30±0.77 CD133-negative vs. 1.14±0.69 CD133-positive cells, P=0.39).

**Conclusion:** Activated human platelets preferentially stimulate the invasion of SP-identified CSCs. Identification of CSC based on both CD133 staining and Hoechst negative SP might be more reliable than using Hoechst SP alone. CD133 positive cells have higher basal levels of MMP-2, but treatment with washed platelet increases MMP-2 levels in CD133 negative, but not positive cells. Platelet treatment does not seem to affect A549 cell MMP-9 levels. Further experiments are required to delineate the role of SDF-1α-CXCR4-MMP signalling in platelet-stimulated cancer stem cell invasion.
CHARACTERIZATION OF eNOS-BASED PLATELET SUBPOPULATIONS IN TRANSGENIC eNOS-GFP MICE

Gabriela Lesyk, Teresa Fong, Paul Jurasz

Background: In vitro studies of human platelets in our laboratory have demonstrated existence of two platelet subpopulations based on the presence or absence of endothelial nitric oxide (eNOS) signaling. We also showed that eNOS-negative (eNOS-ve) platelets lacking eNOS are less abundant (20% of total platelets) and initiate haemostatic reactions in response to collagen. Next, we decided to utilize eNOS-GFP transgenic mice to conduct in vivo studies to verify presence of eNOS-based platelet subpopulations and analyze their haemostatic functions. eNOS-GFP mice express functional human eNOS fused to green fluorescent protein (GFP). This fusion protein enables eNOS detection without intracellular immunostaining of platelets. We hypothesize that eNOS-based platelet subpopulations also exist in transgenic eNOS-GFP mice.

Methods: Mice (14-22 weeks old) were genotyped for GFP expression using qPCR and divided into three groups: WT, eNOS-GFP hemizygous and eNOS-GFP homozygous. Mouse whole blood was obtained by cardiac puncture. Flow cytometry was performed on platelet rich plasma (PRP) after staining with anti-mouse CD41-PerCP-Cy5.5 antibodies specific to GPIIb of platelet fibrinogen receptor. GFP mean fluorescence intensity (MFI) was measured only for CD41+ve events. Dot plots of FL3 (CD41) vs. FL1 (GFP) were created and percentage of GFP+ve events among CD41+ve events was calculated.

Results: GFP MFI for hemizygous and homozygous mice was 9.0±17.45AU (arbitrary units) and 33.8±12.76AU above background fluorescence of WT mouse platelets (N=4, P<0.0114). GFP+ve platelets (CD41+ve events) consisted of 1.41±0.79% in PRP of hemizygous mice and 2.20±0.73% in PRP of homozygous mice.

Conclusion: Preliminary experiments demonstrate presence eNOS-based platelet subpopulations in mice. However, the low amount of GFP+ve (eNOS + ve) platelet in PRP of homozygous mice suggests major species differences in platelet NO-signalling. These differences may in part explain previously reported discrepancies between human and murine platelet NO-signalling data and call into question the utility of mouse models to study platelet eNOS-signalling.
THE VON HIPPEL LINDAU (VHL) PROTEIN DIRECTLY INTERACTS WITH P21 IN A HIF-INDEPENDENT MANNER: A NOVEL MECHANISM WITH IMPORTANT IMPLICATIONS FOR VASCULAR CELL PROLIFERATION AND VASCULAR REMODELLING

Adam Kinnaird, Peter Dromparis, Aristeidis Boukouris, Vikram Gurtu, Bruno Saleme, Sotirios Zervopoulos, Gopinath Sutendra, Evangelos D. Michelakis

**Background:** It is now well accepted that vascular homeostasis and angiogenesis in cardiovascular disease can be regulated by factors other than oxygen levels and HIF activation. A major regulator of HIF levels is VHL, whose main function is thought to be binding and degrading HIF during normoxia. Evidence from cancer suggests that VHL may have HIF-independent effects on p53 target genes, like p21, that are important for the proliferation of vascular cells. We hypothesized that VHL directly binds and degrades p21 independent of HIF.

**Methods:** VHL-deficient cells were transiently (adenoviral) or stably (lentiviral) transduced with VHL. We generated VHL knockout cells using CRISPR/Cas9 genome editing technology. HIF overexpression was achieved using hypoxia or a non-degradable HIF-expressing adenovirus. Co-immunoprecipitations, immunoblots, confocal imaging and siRNA transfections were performed using standard techniques.

**Results:** Transient and sustained VHL overexpression robustly decreased, while knockout of VHL increased p21 mRNA and protein levels. VHL-deficient cells lacking HIF (via siRNA) had unaltered p21. Conversely, VHL and HIF co-expressing cells exhibited low p21 levels compared to VHL-deficient cells. Taken together, these data suggest that VHL-mediated p21 regulation is independent of HIF. VHL over-expression reduced apoptosis (cleaved-caspase-3). Treatment of VHL-expressing cells with MG-132 (proteasome inhibitor) restored p21 to the level of VHL-deficient cells. VHL co-immunoprecipitated with p21 in the presence of MG-132. Induction of p21 and apoptosis was significantly attenuated in over-expressing VHL vs. VHL-deficient cells.

**Conclusion:** These results suggest a physical-interaction between VHL and p21 where VHL degrades p21 via the proteasome. This study suggests a novel mechanism by which vascular cell proliferation could be regulated by VHL, bypassing HIF. This mechanism may be important for both vascular remodeling diseases and cancer (where loss of VHL is associated with common aggressive cancers like RCC).
CLINICAL SCIENCE POSTERS
THE NORWOOD-SANO OPERATION: A COMPARISON OF TWO-YEAR CLINICAL AND NEURODEVELOPMENTAL OUTCOMES BETWEEN PATIENTS WITH CLASSICAL HYPOPLASTIC LEFT HEART SYNDROME AND THOSE WITH VARIANTS

Billie-Jean Martin, I. De Villiers Jonker, Ari R. Joffe, Gwen Bond, David B. Ross, Ivan M. Rebeyka, Charlene M.T. Robertson, Joseph Atallah

Background: Neurodevelopmental outcomes have been suggested by previous studies to be inferior in classic hypoplastic left heart syndrome (HLHS) compared to HLHS variants, following single ventricle palliation. Our objective was to compare survival and neurodevelopmental outcome during the same surgical era in a large, well-described cohort.

Methods: All subjects who underwent a Norwood-Sano operation between April 2005 and December 2012 were included. Follow-up clinical, neurological and developmental data were obtained from the Western Canadian Complex Pediatric Therapies Follow-up Program database. Developmental outcomes were assessed at 2 years of age using the Bayley Scales of Infant and Toddler Development (3rd edition). Survival and outcomes were compared between those with classic vs. variant HLHS. Survival was assessed by Kaplan-Meier analysis.

Results: The study comprised 103 infants (61 male), 65 (43 male) of whom had classic HLHS. All subjects underwent a Norwood-Sano. There were 9 deaths prior to hospital discharge post-Norwood Sano, and an additional 12 interstage deaths. Mortality was the same for classic and variant HLHS (p=1.00). Of the remaining 82, 78 patients underwent second stage (Glenn) palliation, followed by 7 deaths prior to assessment age (3 classic, 4 variants). Four children did not undergo a Glenn, progressing directly to a Fontan (2 variants) or heart transplant (2 classical). Seventy-five patients underwent neurodevelopmental assessment including Bayley-III scores. The mean cognitive composite score was 90.8 vs. 92.6 (p=0.62) and mean motor composite score was 84.5 vs. 88.2 in the classic vs. variant HLHS groups (p=0.29). Neither the cognitive nor motor scores differed between those with classic and variant HLHS (both p>0.05).

Conclusion: In our cohort of patients undergoing a Norwood procedure, survival and neurodevelopmental outcomes at 2 years did not differ between those with classic HLHS vs. variant anatomy.
CHD-CLIN-2

REGIONALIZED SURGICAL CARE: AN IMPORTANT LACK OF ASSOCIATION BETWEEN ON-SITE SURGICAL PROGRAM AND POST-OPERATIVE OUTCOMES IN CHILDREN UNDERGOING FONTAN PALLIATION

Billie-Jean Martin,, Mohammed Al Aklabi, Joyce Harder, John Dyck, Ivan M. Rebeyka, David B. Ross

Background: Complex pediatric cardiac surgery requires coordinated efforts of a team of providers to optimize results. Evidence suggests that outcomes are improved by consolidating care into large volume centers of excellence. Our objective was to determine if outcomes are equivalent in patients across a large regional referral base, or if patients from centers without surgery on site are at a disadvantage.

Methods: Since 1996, all pediatric cardiac surgery has been offered at a single center within the large geographical region assessed. All pediatric patients from 5 referral centers in who underwent a Fontan procedure at this single surgical institute between 1996 and 2014 were included. Follow-up clinical data was obtained from the Western Canadian Children’s Heart Network Database. Outcomes of interest included post-operative length of stay, early mortality, and long term transplant free survival. Baseline characteristics were compared between referring centers and the association between post operative outcomes and home center were assessed using Kaplan-Meier survival analysis and Cox proportional Hazards models.

Results: A total of 279 children (median age 3.3 years, inter quartile range (IQR) 2.8 – 3.9 years; 121 (43.4%) female) underwent a Fontan procedure over the course of the study. Children came from distances of up to 1200 miles away; 105 (37.6%) had the surgical center (Center 1) as their home center. Original cardiac anatomy was hypoplastic left heart syndrome (HLHS) in 102 (36.6%) subjects. Median hospital length of stay was 10 days (IQR, 7-16), and there were 2 early deaths. Median follow-up was 6.6 years (IQR, 3.6 – 12.1 years), There were a total of 16 deaths and 10 transplants over the course of follow-up. Five-year transplant free survival was 92.3%. There was no difference in survival by referral center (Figure; log-rank p=0.53). In multivariable analysis, home center (the surgical center vs others) was not predictive of either LOS (R²=0.53, p=0.75) or transplant free survival (HR 1.41, 95% CI 0.59, 3.40).

Conclusion: In children with complex congenital heart disease, a regionalized care model achieves excellent outcomes, which do not differ according to a patient’s home base. Further study is required to determine the cost effectiveness of this approach as well as impacts on patient and family quality of life.
Transplant-free Survival stratified by Home Center

Time (years)

Center 1  Center 2  Center 3  Center 4  Center 5
REST AND STRESS CINE CARDIAC MRI STRAIN RATE AND AREA PARAMETERS FOR THE DIAGNOSIS OF CORONARY LESIONS IN PEDIATRIC PATIENTS

Jiali Luan, Michelle Noga, Kumaradevan Punithakumar, Edythe Tham

Background: Stress perfusion cardiac MRI (CMR) is a non-invasive method of assessing coronary lesions. Endocardial strain rate and fractional area change (FAC) analysis performed on cine CMR image sequences provides a reproducible method of quantifying myocardial deformation. The objective of this study was to evaluate the diagnostic value of CMR derived strain rate and FAC at rest and stress to detect coronary lesions.

Methods: Nineteen pediatric patients (6-19 years) underwent CMR during rest and adenosine stress for the following indications: 4 Kawasaki disease, 5 arterial switch for TGA, 3 heart transplant, 1 LV dysfunction after tetralogy of Fallot repair, 4 post repair of coronary artery anomalies and 2 chest pain. Twelve patients had coronary lesions defined by coronary angiography, historical surgical intervention or injury. Four chamber cine images were obtained during rest and stress. Longitudinal maximum strain rate (SR) and FAC were calculated using a semi-automated MRI deformation software developed in-house. Ratios (stress/rest) and differences (stress-rest) between stress and rest values were calculated for FAC and maximum SR. Receiver operating characteristic (ROC) curves were generated for each parameter, including the ratios and differences (Table 1). The area under the ROC curve quantifies the effectiveness of the parameter in separating patients with and without coronary lesions. The Mann-Whitney U test was used to assess statistical significance (α=0.05).

Results: The ratio and difference parameters for FAC separated patients with coronary lesions from those without more effectively than individual rest or stress parameters (Table 1). Longitudinal SR ratio and difference parameters separated patients just as well as individual rest/stress parameters. Patients with coronary lesions also had significantly smaller FAC difference and ratio calculations compared to those with no documented coronary lesions. Although not statistically significant, longitudinal SR difference and ratio parameters were smaller for patients with coronary lesions compared to those without. The same cannot be said for individual rest/stress parameters.

Conclusion: Ratio and difference parameters for FAC performed better than individual rest or stress parameters, and may be of discriminatory value in detecting children with coronary lesions. CMR derived myocardial SR is feasible but less discriminatory and may provide a serial method of quantifying contractile reserve in children with suspected coronary abnormalities.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area under the curve</th>
<th>Mann-Whitney p-value</th>
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<td>0.098</td>
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<td>FAC stress</td>
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<td>FAC difference</td>
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<td>Longitudinal strain rate</td>
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<td>Longitudinal strain rate</td>
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FAC = Fractional Area Change
CONGENITAL HEART DISEASE HOSPITALIZATION COSTS IN CANADA

Andrew S. Mackie, Dat Tran, Ariane J. Marelli, Padma Kaul

**Background:** The prevalence of congenital heart disease (CHD) is rising, survivors require life-long care, and late complications are becoming increasingly recognized. The impact of these factors on health care costs is not well understood. We sought to describe inpatient CHD costs among children and adults in Canada from fiscal years 2004-2013.

**Methods:** We conducted an observational retrospective cohort study using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). DAD data was included from all Canadian provinces, except Quebec and the Northern Territories. The DAD includes up to 25 diagnoses, one main and 24 secondary diagnoses. Diagnoses are coded using the International Classification of Diseases (ICD) version 10. We included hospitalizations with a CHD code (ICD-10 Q20.0-26.9) in the main diagnosis field, and hospitalizations having CHD as a secondary diagnosis if the main diagnosis was a co-morbid condition related to CHD. CIHI Patient Cost Estimates were used to provide dollar values. Costs were inflated to 2016 dollar values using a Bank of Canada inflation calculator.

**Results:** 59,917 hospitalizations were included. Patient characteristics are summarized (Table). The estimated annual CHD costs increased by 21.6% from 99.7 million dollars (95% CI 89.4-110.1 million) in 2004 to 121.2 (95% CI 112.8, 129.6) million dollars in 2013 (all values in 2016 Canadian dollars, p<0.001), though median length of stay was stable across the study period. Costs were higher for children compared to adults throughout the study period. However, the cost increase was greater among adults (4.5% relative annual increase, p<0.001) compared to children (0.7% relative annual increase, p=0.006). Adults age 18+ accounted for 38.2% of costs in 2004 vs. 45.8% of inpatient costs in 2013 (p=0.002). Among adults, costs increased among all levels of CHD severity, but to the greatest degree among those with complex CHD (7.2% increase/year, p=0.013). Adult males accounted for increasing costs over time, relative to adult females (p<0.001).

**Conclusion:** Inpatient CHD costs are increasing independent of inflation, particularly among adults with complex lesions. Although children still account for greater inpatient CHD costs, a larger relative increase in costs over time was observed among adults. These data are important in targeting cost containment in an era of fiscal restraint.
<table>
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<th>Characteristic</th>
<th>Children &lt;18</th>
<th>Adults ≥18</th>
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<td>Hospitalizations</td>
<td>38,087</td>
<td>21,830</td>
</tr>
<tr>
<td>Patients</td>
<td>29,363</td>
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<td># hospitalizations per patient</td>
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<tr>
<td>Female (%)</td>
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<td>40.5</td>
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<tr>
<td>CHD severity (%)</td>
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<tr>
<td>Simple</td>
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<tr>
<td>Complex</td>
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</tr>
<tr>
<td>Median LOS in days (IQR)</td>
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</tbody>
</table>

![Graph showing estimated average cost for children and adults from 2004 to 2013 with 95% confidence intervals.](image-url)
CHD-CLIN-5

CARDIOVASCULAR HEALTH IN CONGENITAL HEART DISEASE: THE CANHEART HEALTH INDEX

Kathryn Rankin, Kevin Harris, Christine Voss, Basmina Aminzadah, Ross Gardner, Andrew S. Mackie

Background: The CANHEART Health Index is a composite score of cardiovascular health derived from self-reported health and health behaviours. Individuals with congenital heart disease (CHD) may be at higher risk of acquired cardiovascular disease than the general population due to their underlying physiology and activity restrictions. Our aim was to assess cardiovascular health using CANHEART in youth and adults with CHD.

Methods: We approached patients age 15+ attending cardiology outpatient clinics at BC Children’s Hospital, Stollery Children’s Hospital (AB) or the Mazankowski Alberta Heart Institute (Aug ‘14- Mar ‘16). Participants completed a questionnaire regarding their health behaviours; responses were categorised to ideal/not ideal according to age (youth 15-19 yrs or adults ≥20 yrs) and CANHEART criteria. Adults self-reported diabetes and hypertension. Diagnosis was categorised as: CHD (all types) or structurally normal heart; non-congenital cardiovascular diseases were excluded (n=17). Height and weight were measured and overweight/obesity categorised as BMI ≥25 kg/m^2, or International Obesity Task Force cut-points for those aged <18yrs. CANHEART score was calculated as the sum of individual factors (range: 0-4 in youth; 0-6 in adults), and grouped as poor (≤2 in youth or ≤3 in adults), intermediate (3 in youth, 4-5 in adults) or ideal health (4 in youth, 6 in adults).

Results: We included 206 youth (17.0 ±1.1yrs, 41% female) and 110 adults (35.2±13.1yrs, 47% female) with complete data, of which 44% of youth and 94% of adults had CHD. Most reported to be non-smokers (90% youth vs. 85% adults) and to consume ≥5 servings of fruit and vegetables per day (89 vs. 85%, respectively). More adults than youth reported meeting age-specific physical activity guidelines (83 vs. 55%, p<0.001), however more adults than youth were overweight/obese (51 vs. 23%, p<0.001). In adults, diabetes was rare (<2%) but 20% reported hypertension. The mean CANHEART score was 3.1 (/4) in youth and 4.8 (/6) in adults. In youth, there was no significant difference between those with or without CHD for individual health factors or the prevalence of CANHEART health categories (38% ideal, 39% intermediate and 23% poor). In adults CANHEART score worsened on average by 0.02 points for every additional year of age (p=0.009).

Conclusion: The CANHEART Health Index was similar between youth with and without CHD, with only 1/3 having ideal scores. CANHEART scores worsen with age in adults with CHD, suggesting a need to promote healthy lifestyles during adolescence and throughout adulthood.
HYPOPLASTIC LEFT HEART SYNDROME IS NOT A PREDICTOR OF OUTCOMES FOLLOWING THE FONTAN OPERATION: A COHORT STUDY

Billie-Jean Martin, Mohammed Al Aklabi, Ivan M. Rebeyka, David B. Ross

Background: The anatomy of children with single ventricle physiology has changed since the advent of the Fontan operation, with a significantly greater proportion of those now living with single ventricle having hypoplastic left heart syndrome (HLHS). However, outcomes data for these particular subjects are sparse. Our objective was to determine if there is an association between HLHS anatomy and outcomes following a Fontan operation.

Methods: All pediatric patients from across Western Canada who underwent a Fontan procedure at the University of Alberta Stollery Children’s Hospital (UAH) between 1996 and 2014 were included. Follow-up clinical data was obtained from the Western Canadian Children’s Heart Network Database. Outcomes of interest included post-operative length of stay, early mortality, and long term transplant free survival. Baseline characteristics were compared between those with and without HLHS and the association between post operative outcomes and HLHS were assessed using Kaplan-Meier survival analysis and Cox proportional Hazards models.

Results: A total of 279 children (median age 3.3 years, inter quartile range (IQR) 2.8 – 3.9 years; 121 (43.4%) female) underwent a Fontan procedure over the course of the study. Original cardiac anatomy was hypoplastic left heart syndrome (HLHS) in 102 (36.6%) subjects, double inlet left ventricle in 43 (15.4%), tricuspid atresia in 32 (11.5%), and other in 102. Median follow-up was 6.6 years (IQR, 3.6 – 12.1 years). There were a total of 16 deaths (2 early) and 11 transplants over the course of follow-up. Five-year transplant free survival was 92.3%, 90.6% in those with HLHS vs 93.3% in those without (p>0.05). There was no difference in survival by HLHS (Figure; log-rank p=0.73). In multivariable analysis, HLHS was not predictive of either LOS (median LOS in HLHS 11 days (IQR 8, 17), in non-HLHS 10 days (IQR 7,16)) or transplant free survival (HR 1.15, 95% CI 0.50, 2.65).

Conclusion: Despite their challenging anatomy, subjects with HLHS who survive to the Fontan do no worse with the operation than those with other anatomy. It is possible than any attendant risk associated with HLHS is no longer an issue by the time these subjects are ready for their third stage palliation.
SUPPORTING ADULTS WITH SHORT-TERM CONTINUOUS FLOW VENTRICULAR ASSIST DEVICES: THE EDMONTON EXPERIENCE


Background: Short-term continuous flow VADs (STCF-VAD) are increasingly being utilized to support patients. However, there is a paucity of information regarding the overall outcomes of patients supported with these devices.

Methods: All adult patients supported with an STCF-VAD, namely the Thoratec Centrimag®, between June 2009 and December 2013 were included in this retrospective single centre study.

Results: A total of 35 patients underwent STCF-VAD implantation. One patient was excluded for lack of data. The STCF-VAD was the first VAD implanted in 97% (n=33) of patients and the second VAD implanted in 3% (n=1) of patients. The median age at implant was 53.5y (IQR 43.5, 59) with 77% (n=27) male. Implantation occurred most commonly in the context of an acute coronary syndrome in 26% (n=9), chronic ischemic cardiomyopathy in 18% (n=6) and dilated cardiomyopathy in 12% (n=4). Patients were supported for a median duration of 11d (IQR 5.25, 23.75), with the longest duration being 70d. LVADs were implanted in 44% (n=15), RVADs in 14% (n=5), and BiVADs in 41% (n=14). Prior to implantation, 34% (n=12) of patients were on ECMO. Overall, 18% (n=6) were weaned for ventricular recovery, 12% (n=4) were converted to a long-term VAD, 18% (n=6) underwent orthotopic heart transplantation, and 52% (n=17) died either on the device or within 30-days post-decannulation. One patient was transferred to an institution in another province while still on STCF-VAD support. Forty-five percent (n=15) of patients survived to hospital discharge. In intermediate-term follow-up with a median duration of 51-months (IQR 43, 55), 87% (n=13) of all patients discharged survived.

Conclusion: STCF-VADs at our centre can successfully bridge adult patients to recovery, conversion to long-term device or transplantation, leading to hospital discharge in just under half of cases. Our results occurred in the context of a high-risk population with over one-third of patients supported on ECMO prior to implantation of STCF-VAD. Mortality hovered around 50%, a result consistent with prior reports on STCF-VAD outcomes. Further study is required to elucidate risk factors significantly affecting survival.
OUTCOMES OF PEDIATRIC HEART FAILURE RELATED HOSPITALIZATIONS IN CANADA: 2004-2013

Gitanjali P Mansukhani, Sunjidatul Islam, Andrew S Mackie, Padma Kaul, Paul F Kantor

Background: Heart failure (HF) is an important cause of morbidity and mortality in children with frequent hospitalizations. Recent data have described this problem in the United States. However, there are currently very limited data describing pediatric heart failure hospitalizations (HFH) in Canada. We sought to describe the prevalence, causes and outcomes of HFH in Canada during a contemporary 10-year time frame.

Methods: The Discharge Abstract Database (DAD) of the Canadian Institute of Health information (CIHI) was used to identify all HFH with heart failure as a primary or secondary diagnosis in patients <18 years of age between 2004 and 2013, in all provinces except Quebec.

Results: A total of 4,693 HFH occurred among 3,523 children. Of these, 73.6% (3,457) occurred in children aged <1yr. The annual number of HFH ranged from 435 to 559 (7 to 10 HFH/100,000 children per year). Congenital heart disease (CHD) and cardiomyopathy were associated with 76.1% and 10.5% of HFH respectively. Ventricular septal defect was the most common CHD lesion (33%). Acquired heart diseases (infective and rheumatic) were present in 4.2% of HFH. Median length of stay (LOS) for all HFH was 10.7 days (IQR 4.1 – 28.7) and was highest in the 0-30 day age group at 21.7 days (IQR 8.1 – 46.6). The In-hospital mortality rate was 8.8%, with the majority of deaths occurring during the index hospitalization. Extra-corporeal life support (ECLS) was a relatively common event in this group, occurring in 19.5% of HFH, with ventricular assist-device implantation recorded in only 0.7%. Cardiac transplantation occurred in 1.9%. 68.5% hospitalizations were not associated with any intervention and cardiac surgery occurred in 23.4%. The remaining had surgery and/or cardiac catheterization. The overall annualized hospitalization rate per 100,000 population declined by 3% per year during the study period (rate ratio 0.97, 95% CI 0.96 to 0.98, p<0.001). For patients discharged alive, the cumulative 30-day readmission rate was 12.5%.

Conclusion: Pediatric HFHs in Canada are a high-risk event, occurring mainly in infants. There is a significant risk for death, early readmission after discharge and ECLS. Over the ten-year study period, the annual hospitalization rate has declined in Canada by 3% per year, which differs from the United States, where the rate of HFH is higher (15-17 patient-events per 100,000 population), with a longer length of stay (mean 19.8 days). The crude hospital mortality rates are however similar in both jurisdictions.
CHF-CLIN-3

LEFT VENTRICULAR ASSIST DEVICE SUPPORT PROTECTS AGAINST PATHOLOGICAL REMODELING IN THE LEFT VENTRICLE AND RIGHT VENTRICLE IN PATIENTS WITH DILATED CARDIOMYOPATHY


Background: Heart failure (HF) is a major cause of morbidity and mortality and dilated cardiomyopathy (DCM) is one of the major causes of HF. Left ventricular assist device (LVAD) has emerged as a bridge to transplant therapy. LVADS are also being considered as destination therapy in patients who are not candidates for heart transplantation.

Hypothesis: To define the impact of LVAD therapy on the left ventricle (LV) and right ventricle (RV) remodeling using explanted human hearts with DCM.

Methods: DCM patients without LVAD (n=8; 7M/1F; age 42-54 years) and with LVAD (n=8; 7M/1F; age 44-58 years) were compared to non-failing controls (NFC; n=6; age 39-56 years; 4M/2F). Left ventricular free wall (LVFW) and right ventricular free wall (RVFW) tissues were collected from explanted DCM hearts and NFC hearts within 15 min of explantation. Global mRNA and microRNA expression profiling and structural remodeling were determined in matched cohorts of DCM patients with LVAD and those without LVAD. The mRNAs promoting myocardial hypertrophy and interstitial fibrosis in the LV and RV were determined using a microarray approach. Further, the comparison of micro-RNAs, which are concordant with the hypertrophy and fibrosis promoting mRNA expressions, was analyzed and compared between the LV and RV.

Results: Total gene entities of 1369 (45%) in LV and 556 (70%) in RV were altered without LVAD. LVAD use resulted in the regulation of 374 (12%) and 117 (15%) genes in the LV and RV, respectively. These changes were associated with marked improvements in the LV and RV myocardial hypertrophy and fibrosis. Use of LVAD was associated with significant changes in the hypertrophy promoting genes HBEGF, GLA, HMOX1 and CORIN in LV, SOD 2 in RV, and PDE5A was normalized in both LV and RV. FGF1, SPARC, LOX, DCN was normalized in LV, while TIMP1 was regulated in both LV and RV. In LV, from total of n=36 miRNA that regulated all mRNAs, n=34 (50%) miRNA regulated exclusively mRNAs with LVAD, compared to 18 (27%) with No-LVAD. There were n=16 (24%) common miRNA which regulated mRNAs in both No LVAD and LVAD. In RV, from total of n=130 miRNA that regulated all mRNAs, n=129 (94%) miRNA regulated exclusively mRNAs with No-LVAD, compared to 5 (4%) with LVAD. From total of n=34 miRNA that concordantly regulated mRNAs that promote Hypertrophy. In LV total of n=13(48%) miRNA with No LVAD, n=7 (26%) miRNA were normalized with the use of LVAD, notably in RV from total of n=24 miRNA with No LVAD, n=23 (98%) were significantly normalized with LVAD. From total of n=34 miRNA that concordantly regulated mRNAs that promote Fibrosis. In LV total of n=25 (51%) miRNA with No LVAD, n=3(6%) miRNA were normalized with the use of LVAD, again notably in RV from total of n=12(50%) miRNA with No LVAD, n=11 (46%) were significantly normalized with LVAD.

Conclusion: LVAD reduced pathological remodeling of hypertrophy and fibrosis in the LV and RV which correlates with altered mRNA and miRNA changes controlling multiple pathogenic pathways with a distinct pattern in the RV. Right and left ventricular remodeling are distinct and we have identified multiple possible therapeutic targets for HF.
FUNCTIONAL OUTCOMES AND QUALITY OF LIFE OF DONATION AFTER CIRCULATORY DEATH LUNG TRANSPLANTATION WITH PORTABLE EX-VIVO LUNG PERFUSION

Jessica G.Y. Luc, Kathy Jackson, Justin G Weinkauf, Darren H Freed, Jayan Nagendran

Background: Donation after circulatory death (DCD) has potential to significantly alleviate the shortage of transplantable lungs. Though DCD lungs are seldom utilized given that they have deleterious warm ischemic times and are prone to inferior lung function post lung transplantation (LTx). The Organ Care System (OCS Lung) is the only portable device for ex-vivo lung perfusion (EVLP) that is designed to minimize cold ischemic injury, as such; portable EVLP may have potential to confer benefit in DCD LTx. We sought to evaluate the effect of portable ex-vivo lung perfusion (EVLP) on survival, functional outcomes and quality of life after DCD LTx compared to transplantation of DCD lungs preserved with conventional cold static preservation.

Methods: We performed a retrospective review of DCD experience at a single lung transplant program using a prospective database.

Results: From 2011-2015, 11 DCD LTx were performed at our institution with 7 (64%) that underwent portable EVLP. Compared to conventional cold static preservation, DCD lungs preserved with portable EVLP had a significantly shorter cold ischemic time (161 ± 44 vs. 234 ± 60 minutes, p=0.045), shorter cannulation to perfusion time (38 ± 18 vs. 246 ± 41 minutes, p<0.001), lower grade of PGD at 72 hours post LTx (0 ± 0.5 vs. 2 ± 0.7, p=0.003), similar mechanical ventilation time (55 ± 44 vs. 103 ± 97 minutes, p=0.281) and hospital length of stay (29 ± 11 vs. 33 ± 10 days, p=0.610). 100% of patients were alive at 6 months follow-up post LTx with improved functional outcomes and quality of life compared to pre LTx, though there are no intergroup differences.

Conclusion: Portable EVLP is an effective modality to increase the rate of DCD lung utilization with validated objective evidence of lung function during EVLP that translates to acceptable clinical outcomes and quality of life post LTx. Further studies are required to validate these initial findings in a larger cohort.
GLUTARALDEHYDE TREATMENT OF HOMOGRAFT PATCHES POTENTIALLY INCREASES THE RISK OF RE-COARCTATION POST NORWOOD: A COHORT STUDY

Billie-Jean Martin, Michael Kaestner, Anne Halpin, Ingrid Larsen, David B Ross, Lori West, Ivan M Rebeyka

**Background:** We have previously demonstrated that use of glutaraldehyde to treat homograft patches for arch reconstruction prevents the profound immunologic sensitization that occurs with untreated patches. However, concerns have arisen that resultant changes in tissue characteristics may predispose infants to recurrent obstruction. The objective of our study was to determine if glutaraldehyde treatment of homograft tissues used in neonates undergoing the Norwood procedure increases rates of aortic recoarctation.

**Methods:** All infants who underwent a Norwood-Sano procedure between 2003 and 2010 at the University of Alberta Hospital were included. Cryopreserved pulmonary homografts were used for all arch reconstructions, and starting in June 2005 all homografts were treated with glutaraldehyde prior to use. Complete follow-up was obtained for all subjects including survival, transplant, and all repeat procedure and diagnostic imaging results. A minimum of 5 year follow-up was available on all included. Kaplan-Meier curves were constructed to assess for differences in survival and arch re-intervention over time.

**Results:** A total of 112 infants were included in the study, 86 (77%) of whom had classic HLHS, 71 (63%) male. There were 28 deaths and 7 transplants over the course of follow-up; 1-, 3- and 5-year transplant free survival were 75%, 72%, and 71% respectively. 92 (82%) subjects made it to the Glenn procedure, and 79 (71%) to a Fontan. Twenty-one (19%) subjects required balloon aortoplasty, and 16 (14%) subjects required surgical arch re-intervention. Of those in the study, 81 (72%) had glutaraldehyde treated patches. At five years, transplant free survival was similar in the glutaraldehyde treated and the non-treated groups (69% vs 74%, p=0.65), but freedom from surgical arch re-intervention was lower in the treated group (81% vs 97%, p=0.042) (Figure 1). Rates of any arch intervention (surgical or balloon angioplasty) were equivalent in the two groups (65% treated vs 80% untreated, p=0.19).

**Conclusion:** Glutaraldehyde treatment of pulmonary homografts has no impact on survival post-Norwood, but is associated with increased rates of surgical arch intervention. The advantages of decreased sensitization with glutaraldehyde treatment need to be balanced against the risk of arch re-coarctation.
Freedom from surgical arch reintervention

Number at risk:
- Non-treated: 31, 30, 30, 29, 29, 29
- Treated: 81, 68, 68, 65, 63, 62

Time (years):
- 0, 1, 2, 3, 4, 5

p = 0.042
Background: Coronary artery bypass grafting remains one of the quintessential procedures performed by the cardiac surgeon. Determining the appropriate operative strategy, including choosing graft types and distal anastomosis location, requires intimate knowledge of the coronary artery circulation and the stenoses contained within it. Since the discovery of coronary artery angiography by Dr. F. Mason Sones in 1958, angiography has been the principle tool in order to obtain coronary anatomy. However, the common method of visually assessing coronary artery stenosis has been highly criticized in the literature due to inaccuracy. Most commonly, visual interpretation overestimates areas of higher stenosis and underestimates areas of lower stenosis. Numerous methods have been utilized in order to correct for these errors. Included in these were methods to retrain observers in “quantitative coronary angiographic techniques” in order to yield higher caliber of stenosis measurements and reduce intra- and interobserver variability. In addition, the adjunct use of calipers has been shown to aid in the reduction of interobserver variation. One of the most frequently used and evidence-based methods to determine the severity of coronary artery stenosis is by computer-assisted quantitative analysis. Multiple studies have effectively demonstrated that computers have less variation in assessment than observer variation. Again demonstrated in these studies were common trends to visually over or underestimate lesions dependent on their true severity. The high variability was further exacerbated by the relative inexperience of the observer. These discrepancies were evident with visual observation in many different clinical situations including before and after coronary angioplasty. Multiple other technological methodologies have been used to further refine coronary anatomy stenoses. These include intravascular ultrasound (IVUS), dual-energy digital subtraction, fractional flow reserve (FFR), coronary flow velocity reserve via transthoracic echocardiogram, and CT angiography. These technologies offer various advantages over simple angiography in terms of not only raising the accuracy of our diagnostic capabilities but also allowing us understanding of both the anatomic and physiological consequences of individual stenosis. Despite our plethora of technological advantages, no one tool or methodology has established itself as the optimal solution to coronary anatomy. Disagreements between CT angiography and conventional measurement are common and multifactorial in origin. Some less invasive methods have lower sensitivity and specificity to detect significant stenosis. Digital coronary arteriography has been criticized as adding additional costs to simple visual estimation of stenosis. In addition, in earlier iterations of the computer quantification, there was concern of inaccurate measurements at critically high stenoses.

Methods: The study will be conducted as a survey of cardiac surgery consultants, cardiac surgery residents, cardiology consultants, and cardiology fellows. We will endeavour to obtain ten representatives from each cohort to participate in our study. These participants will be selected from multiple tertiary care centers where both PCI and CAGB are routinely performed. The participants will be shown the same 4 digital print-outs of coronary artery lesions and asked to rate the visualized stenosis to the nearest 10%. The participants will have 30 seconds to assess each picture and will not be allowed the use of calipers as to most accurately reflect select clinical practices. Furthermore, these participants will be asked if they would offer intervention (either PCI or CAGB) to these patients based on the severity of the lesion (assuming other clinical criteria for intervention are met). The participant's visual estimations will be compared to a computer-generated quantitative stenosis value. The estimations will be analyzed for their accuracy as well as to evaluate intra- and inter-speciality variability.
Conclusion: As this study is in its preliminary stages, we do not have any results or conclusions to discuss yet. This study will attempt to discern not only the differences between cardiologists and cardiac surgeons during the visual assessment of severity of coronary artery lesions, but also how this perception affects clinical managements of a unique cohort of patients. The implication of the results of this study are profound in that it has the potential to demonstrate radically different treatment plans for the same population of patients based on basic visual estimation of disease severity. Furthermore, this study will re-evaluate the ability of the heart team to visually assess coronary artery lesions in the contemporary setting. Many of the studies looking at this issue took place in the early days of coronary angiography and may not represent a modern sample and current technologies.
MID-TERM OUTCOMES OF DISTAL AORTIC ARCH REPLACEMENT VIA LEFT THORACOTOMY USING ANTEGRADE CEREBRAL PERFUSION: A RETROSPECTIVE ANALYSIS

Abdelsalam Elhenawy, Colleen Norris, David Zicho, Michael Moon, Roderick MacArthur

Background: Patients with distal aortic arch aneurysms remain a challenging surgical cohort. Expanding treatment options include both open and endovascular approaches to repair. Endovascular strategies remain unattractive in some cases due to arch hypoplasia, angulation, pseudoaneurysm formation, chronic dissection and suboptimal proximal landing zones. Cerebral and spinal cord injury remain a significant morbidity risk to both repair strategies. We present our results of open repair via left thoracotomy using an adjunctive antegrade cerebral perfusion (ACP) protective strategy.

Methods: Over a ten-year interval ending in April 2015, a total of thirty-five consecutive patients with distal aortic arch pathology were repaired via left thoracotomy using cardiopulmonary bypass and deep hypothermia. Pathology includes congenital, connective tissue and degenerative disorders of the distal aortic arch. Patients with Extent II thoracoabdominal aneurysms were excluded. Thirteen (37%) patients presenting for reoperative surgery, fourteen (40%) patients with coarctation of the aorta, and eleven (31%) patients presenting with an acute aortic syndrome.

Results: Twenty-eight of thirty-five (80%) patients received adjunctive ACP for cerebral protection during distal aortic arch reconstruction. Mean age was 48 years (range 16-71 years) with an average hospital length of stay 9.5 days. Their intraoperative perfusion data are shown in Table1. There were no in hospital deaths or patient requirement for permanent dialysis.

Ten patients (29%) received no blood products throughout the entire hospital stay. One patient developed permanent paraplegia peri-operatively and there were no new strokes or any neurological event. The patient developing paraplegia presented with frank rupture and hemorrhagic shock at the time of surgery.

Our one-year and five-year survival are 100% as of the last follow up with a median follow up of 3.8 years, range 0.10 to 10.3 years. During the follow-up period, there has been no evidence for new neurological events, recurrent coarctation or aneurysm formation and no reoperations on the aorta have been required. To the best of our knowledge, this first series reporting antegrade cerebral perfusion through the left thoracotomy approach.

Conclusion: We present the largest case series (left thoracotomy) of open repair of distal aortic arch pathology as a safe and reproducible treatment option. Antegrade cerebral perfusion might be considered as an adjunctive measure in the overall cerebral protection strategy.

Table1: Intraoperative Perfusion Data

Mean time (minutes):

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass (CPB)</td>
<td>205</td>
</tr>
<tr>
<td>Hypothermic circulatory arrest (HCA)</td>
<td>23</td>
</tr>
<tr>
<td>Aortic arch reconstruction</td>
<td>56</td>
</tr>
<tr>
<td>Antegrade cerebral perfusion (ACP)</td>
<td>33</td>
</tr>
<tr>
<td>Lowest bladder temperature (Celsius)</td>
<td>20</td>
</tr>
</tbody>
</table>
Background: Primary prevention implantable defibrillators (ICD) are under-utilized despite, multiple clinical trials that have demonstrated that they reduce mortality and are cost-effective in patients at risk for sudden cardiac death (SCD). Our aim was to determine physician knowledge about primary prevention ICD indications and to identify potential barriers which may impact their decision to refer for device implantation.

Methods: The Cardiovascular Arrhythmia and Stroke Working Group of Alberta Health Services Cardiovascular Strategic Clinical Network developed a brief web-based survey to aid in the design of a complex device care pathway. General Internists and Cardiologists with Alberta Medical Association membership and Cardiology residents in Alberta were given five case scenarios regarding primary prevention ICD indications and asked about perceived barriers for ICD referral. The case scenarios were based on current device guidelines.

Results: The survey was completed by 109 of 799 (response rate of 14%) physicians who received a survey link. The majority of respondents were General Internists (55%), with fewer Cardiologists (32%) and Cardiology residents (13%). Among the physicians, 62% were male; 41% were < 40 years, 28% were 41-50 years and 31% > 50 years. The majority of physicians practiced at a University Hospital (66%) while the remainder (24%) practiced at a Community Hospital or as part of a Primary Care Network (10%). In terms of years of independent practice, 17% had < 1 year, 26% 1-< 5 years, 13% 5-10 years and 44% > 10 years. Case scenarios were all answered correctly by 90% of Cardiologists, 81% of Cardiology residents and 66% of General Internists (p=0.038). Overall, the most common barriers to ICD referral were concerns regarding the understanding of indications for a primary prevention ICD (47%), the risk of inappropriate shocks (41%) and cost-effectiveness of device therapy (55%). There were significant differences regarding perceived barriers for an ICD referral among the physician groups (p<0.0001, Figure 1). The most common barriers were concerns about cost-effectiveness for Cardiologists (54%), concerns about the risk of inappropriate shocks for Cardiology residents (64%) and knowledge about ICD indications for General Internists (60%).

Conclusion: Physician knowledge and perceived barriers for referral of a primary prevention ICD varies among physician groups who may encounter patients at risk for SCD. Addressing these different perceived barriers is important prior to implementation of a complex device care pathway.
Figure 1. Identified barriers for a primary prevention ICD referral according to physician group.
EP-CLIN-2

PRACTICE PATTERNS OF ORAL ANTICOAGULANTS FOR ATRIAL FIBRILLATION ON TERTIARY CARE CARDIOLOGY UNITS

Caitlyn Thomson, Lily Zhu, Taryn Heck, Glen Pearson, Sheri Koshman

Background: Oral anticoagulants (OACs) for stroke prophylaxis in non-valvular atrial fibrillation (NVAF) have been evolving rapidly since Health Canada's approval of direct oral anticoagulants (DOACs). Data on the utilization of these newer OACs in the management of NVAF is currently lacking. The aim of this study was to evaluate current practice patterns of OACs, on admission and upon discharge from hospital, assessing whether admission to a cardiology unit impacts the use of OACs.

Methods: A retrospective chart review was conducted of randomly selected patients admitted to tertiary care cardiology units between January 1st, 2013 and December 31st, 2015. Patients were identified via medical records using the ICD-10 I48 code. Adult patients were included if they had NVAF, a CHADS2 score ≥ 1, were on an OAC at admission, and discharged to their primary residence. Patients were excluded if they were on an OAC for a reason other than NVAF. Data regarding patient demographics, OACs on admission, changes made to OACs and documented reason for changes was collected. A research electronic data capture program (REDCap™) was used to capture and analyze the data. The primary outcome was to determine the proportion of patients on a Vitamin K antagonist (VKA) or a DOAC on admission to hospital.

Results: Of the 460 charts screened, 208 (45%) charts were eligible for inclusion. The most common reasons for exclusion were CHADS2 score <1 (15.5%) and no OAC on admission in those with a CHADS2 score >1 (38.6%). The majority of patients were male (71.2%), with an average age of 73 (+/-5) years, and a mean CHADS2 score of 2.3 (+/-1.1). On admission, 55.6% and 44.4% of patients were on a VKA and DOAC, respectively. Only 17.4% of patients were discharged on a different OAC than they were admitted on. The majority of these changes were from one DOAC to another DOAC (47.2%). Notably, 38.9% and 13.9% represented, switching from a VKA to DOAC and DOAC to VKA, respectively. Of those discharged on a different OAC, 19.3% did not have their prescription filled within 14 days of discharge.

Conclusion: In this “real world” study of the practice patterns of OACs in a Canadian tertiary care centre, more than half of patients were admitted on warfarin. Switches between OACs rarely occurred in the hospital setting, and when they did majority were from a DOAC to another DOAC or from a VKA to a DOAC.
THE ASSOCIATION BETWEEN ALTITUDE OF COUNTRIES AND CORONARY ARTERY DISEASE-RELATED MORTALITY: AN ECOLOGICAL STUDY

Yongzhe Hong, M. Sean McMurtry

Background: Residing in high altitude has been considered as a protective factor for coronary artery disease (CAD). In a prospective study, a reduction in coronary mortality was observed in residents living at high altitude compared to those living at sea levels, after adjusting for cardiovascular risk factors. However, no prior study regarding the association between altitude and CAD mortality was conducted in a national level. We aimed to investigate the association between the average altitude of countries and CAD-related mortality, adjusting for common cardiovascular risk factors and health expenditure.

Methods: This was an ecological study design whose unit of observation is on aggregate level. The data on the average altitudes of each country were obtained from the Country Geography Data in Portland State University. Country-level data on CAD-related risk factors, health expenditure and mortality were extracted from World Health Organization (WHO) Health Statistics and Information Systems. Considering the availability of most up-to-date information and adequate samples, countries which have available data of CAD-related mortality in 2009 were included for analysis. The data of mortality, the only version of standardized death rate of both sexes and all age, had been standardized by WHO to standard population. Common cardiovascular risk factors include prevalence of hypertension, smoking, high cholesterol and diabetes. All prevalence covariates were age-standardized rate with a unit of percent. Multiple linear regression models were used to assess the association between CAD-related mortality and the national average altitude.

Results: There were 55 countries being analyzed. The average altitude of 55 countries was 484.10 (95%CI 370.37, 597.83). No clear correlation was observed between elevation and CAD-related age-standardized death rate. And the association between them was not significant in univariate analysis. (P-value=0.60, 95%CI -0.11, 0.06) Multiple linear regression with the highest R-squared 0.71 demonstrated that there was not significant statistical association between average altitude and age-standardized mortality, after adjusting for prevalence of hypertension, raised blood glucose, cholesterol, smoking and health expenditure per capita. Therefore, a post hoc power analysis was performed. The power of this statistical test was 0.14.

Conclusion: The negative results we found between average elevation and CAD-related age-standardized mortality were subjected to 87% type II error based on a power of 0.14. We were not able to augment the sample size due to the limited available data from WHO.
EPI-CLIN-2

IMPACT OF PRETERM BIRTH ON LEFT VENTRICULAR MASS AND FUNCTION IN ADOLESCENCE

Abbas Hyderi, Michael Stickland, Ian Adatia, Lisa Hornberger

Background: Preterm birth (PB) is defined as birth < 37 weeks and is a major cause of mortality and morbidity. 10 % of all births are Preterm births and with advances in perinatal care, there is a growing population of preterm infants entering adolescence/adulthood. This growing sub-population and their cardiovascular health (CV) have been poorly studied. Left Ventricular (LV) indices such as LV mass/function are critical in understanding their long term CV health. Preterm infants are born with structurally and functionally immature organ systems. This immaturity leads to ‘adaptations/programming’ required for survival, albeit they may alter their future potential/disease. Fetal circulation is characterized by a ‘low resistance’ circuit, and as loading conditions abruptly changes at delivery, the preterm heart accommodates to ‘high afterload. As a result, there is cardiac ‘remodeling’ including switching from fetal hyperplastic cardio myocytes to accelerated hypertrophic pattern. Various models have demonstrated increased myocardial collagen/fibrosis as a response. This altered architecture (remodeling) may have potential for long term consequences in the preterm infant’s heart. Furthermore, we have previously demonstrated that LV diastolic function is abnormal in preterm < 32 weeks compared to term controls and we also noted they do not ‘resolve by Term age equivalent. Although, there is paucity of data regarding long term CV health of adults born preterm, some data already suggests reduced CV health markers (higher Blood pressure, increased LV mass index, LV reduced function, etc). Lastly, using state of art CV tools like Speckle tracking imaging (STE) and Torsion to assess LV health is still novel in this specific sub-population.

Hypothesis: Adolescent’s born prematurely will have increased LV mass and impaired LV function (both systolic and diastolic).

Methods: This study is part of New Breath study at University of Alberta. Adolescents born extremely premature (< 28 weeks) during 1997-2000 were recruited in 2012. Detailed clinical evaluations and cardiopulmonary assessments (Echo & STE) were performed. Controls were healthy Adolescents -age and sex matched but born > 37 weeks. Overall, 66 patients included with 38 cases and 28 controls were studied. Results are being analyzed using standard Statistical packages (SPSS). We applied student ‘t’ test and other standard statistical tests including standard deviation, confidence interval and p < 0.05 considered to be significant.

Results: Preliminary results have shown some interesting, yet subtle differences especially in Basal and Inferior segments both in Longitudinal and Circumferential strain patterns. Rest of Data is currently being analyzed.

Conclusion: Very Preliminary results suggest a trend towards subtle LV dysfunction in basal & Inferior LV segments. Further analysis and detailed study required to arrive at a Conclusion.
THE EFFECTIVENESS OF PHARMACIST INTERVENTION ON CARDIOVASCULAR RISK. THE MULTICENTER RANDOMIZED CONTROLLED RXEACH TRIAL

Ross T Tsuyuki, Yazid N Al Hamarneh, Charlotte A Jones, Brenda R Hemmelgarn

**Background:** Despite the risk associated with hypertension, diabetes, dyslipidemia, and smoking, these cardiovascular disease (CVD) risk factors remain poorly identified and controlled.

**Objectives:** To evaluate the effect of a community pharmacy-based case finding and intervention program on estimated cardiovascular risk.

**Methods:** Design: Randomized controlled trial. Setting: 56 community pharmacies across Alberta. Population: Adults at high risk for CVD events, including those with diabetes, chronic kidney disease, vascular disease and/or Framingham score > 20% who have at least one uncontrolled risk factor (hypertension, LDL-cholesterol (LDL-c), HbA1c, or current smoking).

Randomization: Participants were randomized (1:1 basis) into advanced or usual care groups.

Advanced care: Pharmacists provided participants with physical and laboratory assessments, individualized CVD risk assessment and education, pharmacists prescribed where appropriate to achieve treatment targets, regular monthly follow-ups for 3 months. Usual pharmacist care occurred with no specific intervention for 3 months. Primary outcome: The difference in change in estimated CVD risk between advanced and usual care groups, calculated using a relevant risk calculator based on participants’ co-morbidities (Framingham, International, or UKPDS).

**Results:** We enrolled 723 patients. Median age was 62 years (interquartile range 54-69), 57% were male and 27% were smokers. After adjusting for baseline values, the difference in change in CVD risk was 21% (p<0.001): a change of 0.2 mmol/L in LDL-c (p<0.001), 9.4 mmHg in systolic blood pressure (p<0.001), 0.92% in HbA1c (p<0.001), and 20.2% in smoking cessation (p=0.002) between advanced and usual care groups

**Conclusion:** This is the first large randomized trial of CVD risk reduction in community pharmacy settings. Patients in the advanced care group were 21% less likely to have a heart attack, stroke, or peripheral artery disease when compared to those in the usual care group. RxEACH provides evidence for the benefit of pharmacist care on both global CVD risk and individual risk factors.
EPI-CLIN-4

CARDIAC REHABILITATION IN SUBJECTS WITH PERIPHERAL ARTERIAL DISEASE: A HIGHER RISK PATIENT POPULATION WHO BENEFIT FROM ATTENDANCE

Billie-Jean Martin, Trina Hauer, Leslie Austford, Ross Arena, Alan Hirsch, James Stone, Sandeep Aggarwal

Background: Peripheral vascular disease (PAD) is a common co-morbidity in subjects with coronary artery disease referred for cardiac rehabilitation (CR). However, little is known about the impact of PAD on CR attendance or outcomes.

Methods: This study included all subjects who were referred to a 12-week, exercise based CR program in Calgary, Canada between 1996 and 2013. Baseline patient characteristics including age, sex, and clinical characteristics were compared between those who completed CR and did not. Rates of attendance and completion were compared by PAD, as was change in exercise capacity measured by exercise testing over the course of CR for all those who completed the program. Unadjusted and adjusted (for all available clinical covariates) Cox proportional hazard models were constructed to assess the association between CR completion and mortality. Models were stratified by PAD diagnosis.

Results: A total of 15927 subjects were referred to CR; of those, only 894 (5.6%) had a formal diagnosis of PAD. Subjects with PAD were less likely to complete CR (44.4 vs 55.6% for non-PAD, p<0.0001), and more likely to drop out if they started (23.8 vs 17.2%, p<0.0001). PAD patients also achieved a lesser improvement in exercise capacity over the course of CR (0.76 vs 0.90 METs, p=0.0029). There were 1569 deaths over the course of follow-up; 5 year survival was lower in those with PAD (87.9 vs 94.9%) (Figure). CR attendance was associated with a similar reduction in mortality for those with (HR 0.62, 95%CI 0.44, 0.85) and without (HR 0.55, 95%CI 0.49, 0.61) PAD in adjusted models.

Conclusion: Subjects with coexisting PAD in a CR program have a higher mortality and thus are a higher risk CR group. They derive significant mortality reduction from attending CR even though they have less improvement in their exercise capacity. They are, however, less likely to attend and more likely to drop out. Removing barriers to CR attendance and completion is important for those suffering from PAD.
The Kaplan-Meier survival estimates show the probability of remaining alive over time for different groups. The x-axis represents time in years, while the y-axis indicates survival probability. The table below lists the number at risk for each group at various time points:

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CR, No PAD</td>
<td>5779</td>
<td>5290</td>
<td>3240</td>
<td>1799</td>
<td>814</td>
<td>224</td>
</tr>
<tr>
<td>No CR, PAD</td>
<td>497</td>
<td>352</td>
<td>228</td>
<td>127</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>CR, no PAD</td>
<td>3253</td>
<td>2799</td>
<td>4822</td>
<td>3122</td>
<td>1550</td>
<td>510</td>
</tr>
<tr>
<td>CR, PAD</td>
<td>397</td>
<td>269</td>
<td>211</td>
<td>125</td>
<td>52</td>
<td>14</td>
</tr>
</tbody>
</table>

Survival curves are represented as follows:
- Dashed line: No CR, No PAD
- Dotted line: No CR, PAD
- Solid line: CR, No PAD
- Dashed-dotted line: CR, PAD
Background: Early detection of chronic kidney disease (CKD) can help optimize treatment and delay the progression of kidney disease. The CKD Pathway (www.ckdpathway.ca) was developed to provide evidence-based guidance on targeted screening and management of these high risk patients.

Objective: To evaluate the use of the CKD Pathway by pharmacists in identifying CKD.

Methods: This evaluation was conducted as part of the RxEACH study, a randomized study of a pharmacist-led cardiovascular disease (CVD) risk reduction intervention vs usual care

Setting: 56 Community pharmacies across Alberta. Population: Individuals at high risk for CVD, including those with diabetes, vascular disease, Framingham risk >20% and/or a history of CKD. Intervention: Pharmacists used the CKD Pathway targeted screening guidelines to screen all individuals, performing a serum creatinine (and estimated glomerular filtration rate [eGFR]) and random urine albumin to creatinine ratio (ACR). Primary outcome: Proportion of patients with previously unrecognized CKD, defined as, no previous diagnosis of CKD as reported by the patient and/or recognized by the pharmacist (and confirmed by laboratory results), and having 2 consecutive eGFRs both <60 mL/min/1.73 m2 and/or 2 consecutive ACRs both ≥3 mg/mmol or one ACR ≥30 mg/mmol over a 3-month period.

Results: We enrolled 723 patients in RxEACH, of whom 290 met the criteria for CKD. Of these 290 patients, 41% (n=119) had previously unrecognized CKD. Eighty-five percent of these unrecognized cases were identified via ACR.

Conclusion: Community pharmacists' application of the CKD pathway in patients at high risk for CVD events demonstrated a high prevalence of unrecognized CKD. These results suggest that pharmacists, supported by the CKD pathway, are in a unique position to undertake targeted screening, which represents promising approach that has implications for chronic disease prevention and management. This also highlights the value and impact of judicious ordering of laboratory tests by pharmacists.
IMPACT OF COMPLETE REVASCULARIZATION IN ACUTE CORONARY SYNDROMES:
INSIGHTS FROM THE ALBERTA CONTEMPORARY ACUTE CORONARY SYNDROME
PATIENTS INVASIVE TREATMENT STRATEGIES (COAPT) REGISTRY

Arjun Gupta, Padma Kaul, Wendimagegn Alemayehu, Paul W. Armstrong,
Robert C. Welsh, Kevin R. Bainey

Background: Controversy exists regarding the benefits of complete revascularization (CR)
compared to incomplete revascularization (IR) in acute coronary syndrome (ACS) patients
with multi-vessel disease (MVD) undergoing percutaneous coronary intervention (PCI).
Whereas recurrent cardiovascular events may occur more often following IR, additional
intervention is required for CR which exposes patients to the risk of further procedures. Using
a large provincial ACS registry, we examine the incidence, demographic profile and clinical
outcome of ACS patients with MVD comparing IR to CR.

Methods: We evaluated 5181 ACS patients with MVD (≥70% stenosis in 2 or more vessels)
hospitalized with an ACS undergoing PCI in Alberta, Canada between April 1 2010 and March
31 2013. Patients with prior coronary artery bypass grafting (CABG) surgery were excluded.
Comparisons were made between patients who underwent CR (APPROACH jeopardy score
≤10%) within 3 months from index PCI versus patients with IR (APPROACH jeopardy score
> 10%). One year outcomes in the primary composite of death or recurrent myocardial
infarction (MI) and secondary composite of death, recurrent MI or repeat revascularization
were explored. Logistic regression models were used to examine the multivariable-adjusted
association between revascularization status and clinical outcome.

Results: Of the study cohort, 61.5% received CR. These patients were younger and less
likely to have diabetes or prior cardiovascular conditions (Table). Independent predictors
of CR included age (per 10 years) (adjusted odds ratio [OR] 0.84, 95% confidence interval
[CI] 0.80-0.89), sex (female vs. male: OR 1.17, 95%CI 1.02-1.35), diabetes (adjusted OR
0.77, 95% CI 0.67-0.87), prior MI (adjusted OR 0.64, 95% CI 0.52-0.78), prior heart failure
(adjusted OR 0.59, 95% CI 0.48-0.74), and ACS presentation (Non ST-elevation MI versus
unstable angina: adjusted OR 0.94, 95% CI 0.77-1.15; ST-elevation MI versus unstable
angina: adjusted OR 0.81, 95% CI 0.66-0.99). One year death occurred less frequently
with CR (2.5% versus 7.5%, p<0.0001; adjusted OR 0.38, 95% CI 0.28-0.51). Similarly, one
year recurrent MI was less likely with CR (2.5% versus 7.5%, p<0.0001; adjusted OR 0.38,
95% CI 0.28-0.51). Both primary and secondary composite outcomes were reduced with
CR (Table) (primary composite adjusted OR 0.42, 95% CI 0.33-0.53; secondary composite
adjusted OR 0.45, 95% CI 0.39-0.53).

Conclusion: Results from this large contemporary registry of ACS patients with MVD
undergoing PCI suggests CR occurs commonly and is associated with improved clinical
outcome at one year. Given the potential for unmeasured confounders, our findings deserve
confirmation in other data sets and appropriately powered randomized trials.
Table

<table>
<thead>
<tr>
<th></th>
<th>Complete Revascularization (n=3190)</th>
<th>Incomplete Revascularization (n=1991)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean,SD)</td>
<td>62.0 (11.5)</td>
<td>64.6 (12.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex (female) (%)</td>
<td>23.3</td>
<td>23.0</td>
<td>0.7911</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23.8</td>
<td>29.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prior cardiovascular conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI (%)</td>
<td>7.3</td>
<td>11.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>5.5</td>
<td>10.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>5.9</td>
<td>8.1</td>
<td>0.002</td>
</tr>
<tr>
<td>ACS presentation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unstable angina (%)</td>
<td>10.4</td>
<td>9.6</td>
<td>0.356</td>
</tr>
<tr>
<td>Non ST-elevation MI (%)</td>
<td>42.7</td>
<td>40.7</td>
<td>0.159</td>
</tr>
<tr>
<td>ST-elevation MI (%)</td>
<td>46.9</td>
<td>49.7</td>
<td>0.051</td>
</tr>
<tr>
<td>Clinical Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Death/recurrent MI (%)</td>
<td>3.8</td>
<td>10.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Secondary Death/recurrent MI/repeat revascularization (%)</td>
<td>7.2</td>
<td>18.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome, MI=myocardial infarction, SD=standard deviation
ETHNIC AND SEX DIFFERENCES IN AMBULANCE ACTIVATION AMONG HOSPITALIZED PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION

Arjun Gupta, Padma Kaul, Wendimagegn Alemayehu, Robert C. Welsh, Kevin R. Bainey

Background: Emergency medical service (EMS) activation has become an integral component in managing ST-elevation myocardial infarction (STEMI) patients. Within an integrated STEMI system of care, emergency transfer by EMS reduces ischemic time with implementation of rapid reperfusion protocols, yet EMS activation remains under-utilized. The current study examines whether EMS activation varies by ethnicity or sex among a large provincial cohort of hospitalized STEMI patients.

Methods: Patients > 18 years of age hospitalized with a primary diagnosis of STEMI in Alberta between April 1 2007 and March 31 2013 were included. Previously validated naming algorithms were used to categorize patients according to ethnicity (Caucasian, Chinese, South Asian, or Other Asian [Filipino, Japanese, Vietnamese, Korean]). Unadjusted rates of presentation by EMS (ground ambulance) versus self-presentation were compared across ethnic groups and by patient sex. Multivariable logistic regression was used to determine whether ethnicity and sex were independently associated with EMS presentation, after accounting for other demographic characteristics and co-morbid conditions.

Results: Of the 11,972 STEMI patients, 50.2% (n=6014) presented to hospital via ambulance. Compared with self-presenters, patients presenting to hospital with EMS were older (66.7 years vs. 61.8 years p<0.001), more commonly female (33.1% vs. 23.9%, p<0.001) and had prior cardiovascular conditions (myocardial infarction: 7.1% vs. 6.2%, p=0.055; heart failure: 14.5% vs. 8.0%, p<0.001; atrial fibrillation: 10.1% vs. 6.4%, p<0.001). Differences in ethnic EMS activation were noted (Caucasian 50.0% [5771/11541] vs. Chinese 60.0% [88/147] vs. South Asian 57.0% [110/192] vs. other Asian 49.5% [45/91], p=0.026). After adjustment, both ethnicity and gender remained independent predictors of EMS activation (Figure).

Conclusion: In a provincial cohort of patients presenting to hospital with STEMI, activation of EMS appears suboptimal and differs by ethnicity and sex. Further efforts are required to address these disparities in order to enhance public awareness of ambulance activation for chest pain.
Figure: Adjusted Plot of Ambulance Activation According to Sex and Ethnicity*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>1.31 (1.20-1.42)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese vs. Caucasian</td>
<td>1.46 (1.04-2.05)</td>
</tr>
<tr>
<td>South Asian vs. Caucasian</td>
<td>1.52 (1.14-2.04)</td>
</tr>
<tr>
<td>Other Asian vs. Caucasian</td>
<td>1.01 (0.66-1.55)</td>
</tr>
</tbody>
</table>

0.1 less likely to activate EMS  1 more likely to activate EMS  10

*Adjusted for age, myocardial infarction, heart failure, cerebrovascular disease, dementia, obstructive airways disease, diabetes, chronic renal failure, cancer, atrial fibrillation.
IHD-CLIN-3

BLEEDING AND TRANSFUSION RATES IN A CONTEMPORARY CANADIAN STEMI POPULATION

Debraj Das, Anamaria Savu, Kevin R. Bainey, Robert C. Welsh, Padma Kaul

Background: Anti-thrombotic therapy remains essential in the treatment of ST-elevation myocardial infarction (STEMI) both in the acute setting and during chronic secondary prevention. With advances in these agents including enhanced potency, ischemic events continue to decline at the cost of increasing bleeding risk. Using a large Canadian population health data base, we evaluated the temporal impact of anti-thrombotic agents on in-hospital bleeding and transfusion rates in STEMI.

Methods: Data obtained from the Canadian Institutes of Health Information (CIHI) included patients >20 years of age hospitalized for STEMI between April 2007 and March 2014 across all Canadian acute care facilities, except Quebec.

Results: We excluded patients with missing identification (1662 patients) and those receiving coronary artery bypass grafting (927 patients) leaving us with 118 816 index hospitalizations for STEMI. Baseline characteristics of patients more likely to have in-hospital bleeds or receive blood transfusions were individuals who were older, diabetic, hypertensive and had congestive heart failure. These patients had increased lengths of stay and were more likely to die in hospital (Figure 1). Between April 2007 and March 2014, both in-hospital bleeding (any) and major bleeding rates declined (3.0% to 2.2%, p<0.0001; 2.0% to 1.4%, p<0.0001 respectively). A decline in the blood transfusion rates was also observed (3.8% to 3.1%, p<0.0001) (Figure 2). In patients receiving primary PCI only (i.e. no fibrinolysis), a decline in bleeding (any) and major bleeding was similarly demonstrated (3.0% to 2.0%, p<0.0001; 1.9% to 1.5%, p<0.0001 respectively).

Conclusion: Bleeding and blood transfusion rates have decreased over the past 7 years in all Canadian STEMI patients despite advances in anti-thrombotic pharmacotherapy. With the evolving landscape of modern STEMI management, this decline may be reflective of enhanced awareness of bleeding complications with operator strategies employed to mitigate risk. Further exploration is required to identify practice patterns used to protect patients from bleeding events.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Bleeding</th>
<th>In-hospital Bleeding*</th>
<th>No Blood Transfusion</th>
<th>In-hospital Blood Transfusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>115749</td>
<td>3067</td>
<td>114738</td>
<td>4078</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>63.3 (13.5)</td>
<td>70.2 (12.8)</td>
<td>63.3 (13.5)</td>
<td>70.9 (12.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>82952 (71.7)</td>
<td>2091 (68.2)</td>
<td>82843 (72.2)</td>
<td>2200 (53.9)</td>
</tr>
<tr>
<td>Discharged dead, n (%)</td>
<td>6266 (5.4)</td>
<td>545 (17.8)</td>
<td>5793 (5.0)</td>
<td>1018 (25.0)</td>
</tr>
<tr>
<td>Length of Stay, d mean, SD</td>
<td>4.4 (7.6)</td>
<td>11.2 (14.9)</td>
<td>4.3 (7.1)</td>
<td>14.4 (18.0)</td>
</tr>
<tr>
<td>Charlson Score = 0 (%)</td>
<td>76447 (66.0)</td>
<td>1098 (35.8)</td>
<td>76335 (66.5)</td>
<td>1210 (29.7)</td>
</tr>
<tr>
<td>Charlson Score = 1, 2 (%)</td>
<td>30551 (26.4)</td>
<td>1229 (40.1)</td>
<td>30187 (26.3)</td>
<td>1593 (39.1)</td>
</tr>
<tr>
<td>Charlson Score = 3, 4 (%)</td>
<td>7469 (6.5)</td>
<td>582 (19.0)</td>
<td>7071 (6.2)</td>
<td>980 (24.0)</td>
</tr>
<tr>
<td>Charlson Score = 5+ (%)</td>
<td>1282 (1.1)</td>
<td>158 (5.2)</td>
<td>1145 (1.0)</td>
<td>295 (7.2)</td>
</tr>
</tbody>
</table>

*All comparisons between bleeding and no bleeding and between blood transfusion and no blood transfusion groups are statistically significant at p<0.01.
CANADIAN STEMI PATIENTS WITH BLEEDING OR BLOOD TRANSFUSION BETWEEN APRIL 2007 AND MARCH 2014

NUMBER OF PATIENTS

YEAR

2007 2008 2009 2010 2011 2012 2013

Bleed Major Bleed Blood Transfusion
IMG-CLIN-1

A NOVEL APPROACH TO MULTI-VIEW FUSION OF PARA斯特ERNAL AND APICAL 3D ECHOCARDIOGRAPHY DATASETS USING OPTICAL TRACKING

Kumaradevan Punithakumar, Abhilash Hareendranathan, Alexander McNulty, Marina Biamonte, Allen He, Michelle Noga, Pierre Boulanger, Harald Becher

Background: For many years, 3D echocardiography has been available and offers a very fast and efficient way of scanning the heart. However, because there are still limitations such as spatial resolution, signal to noise ratio, and field-of-view with current 3D echocardiographic scanners, the potential of 3D echocardiography is not yet exploited in patients undergoing transthoracic echocardiography. To improve image quality and field-of-view in 3D echocardiography, a novel approach for the fusion and processing of multiple 3D echocardiography images is proposed using an optical tracking system.

Methods: The proposed method incorporates breath-hold position tracking to infer that the heart remains at the same position during different acquisitions [1]. Using geometric transformations and a new wavelet-based fusion algorithm the 3D datasets were processed into a single 3D dataset. A qualitative study was conducted to evaluate the following clinically relevant parameters from the image: 1) clarity of myocardial border; 2) noise level of the image; 3) contrast of the image; 4) sharpness of the image; and 5) clarity of the leaflet (if present) by presenting parasternal, apical and fused views to a cardiologist and a sonographer in random order.

Results: In six healthy male volunteers 18 pairs of apical/parasternal 3D ultrasound datasets were acquired during a single as well as in subsequent breath-holds. The proposed method yielded a field-of-view improvement of 35.4% ± 12.5% with a significant improvement in contrast (66.5% ± 21.7%), contrast-to-noise ratio (49.9% ± 28.7%) and signal-to-noise ratio (57.6% ± 47.9%) in comparison to single 3D recordings (p < 0.001). On a scale of 1 to 4, our method yielded the following scores: 3.33 ± 0.88 (myocardial border); 3.20 ± 0.92 (noise level); 3.43 ± 0.89 (contrast); 3.20 ± 1.03 (sharpness); and 3.48 ± 1.03 (leaflet clarity), the highest scores in comparison to single views as well as previous image processing based methods.

Conclusion: The first study on humans fusing 3D echocardiograms in a clinical setting showed that the proposed method of multi-view fusion using optical tracking is feasible and results in improved field-of-view and image quality.

References
ASSESSMENT OF A NEW CARDIAC REHABILITATION PROGRAM

David Buijs, Andrea Van Damme, Kara Penney, Gabor Gyenes

Background: In those with established cardiac conditions comes an increased risk of future morbidity and mortality. Traditional exercise based cardiac rehabilitation (CR) programs that consist of bi-weekly exercise sessions have been shown to reduce this risk. However, with the increasing age of the population the incidence and prevalence of cardiac conditions continues to grow and with it a concomitant demand for CR. In order to meet this growing demand some CR programs have reduced the frequency of exercise sessions and supplemented them with home exercise guidelines. However, little evidence exists on the impact of this program model on the exercise capacity of cardiac patients. Therefore, the purpose of this study was to determine the impact of this new program model on the exercise capacity of cardiac patients.

Methods: Participants were recruited from patients referred to the Northern Alberta Cardiac Rehabilitation Program between May and December 2015. Exercise capacity was assessed using a symptom limited exercise test and peak metabolic equivalents (METs) achieved were calculated. Patients then participated in an 8 week CR program that included weekly exercise sessions and group education classes focusing on their cardiac risk factors. The exercise sessions consisted of 30-40 minutes of aerobic exercise at a moderate intensity (i.e., 70-85% of peak heart rate achieved on the baseline test) as well as light resistance training (i.e., 10-15 reps, 1-3 sets for major muscle groups). A home exercise diary was given with guidelines to exercise at least > 150 minutes per week at a moderate intensity. Testing was repeated upon program completion. Descriptive data is expressed as mean + SD or frequency. To determine the impact of the program on exercise capacity a paired sample t-test was used.

Results: Forty-one patients were recruited (M:F, 38:3; mean age 60 + 11 years). Primary diagnosis’ included coronary artery disease (CAD) (n=27), valvular disease (n=5), both CAD and valvular (n=4), heart failure (n=3), Wolf-Parkinson-White (n=1) and myocarditis (n=1). Participants completed 90% of the exercise sessions and demonstrated a significant increase in their exercise capacity (8.7 + 2.5 METs vs 10.1 + 2.8 METs; p < 0.05).

Conclusion: An 8 week CR program of weekly exercise sessions supplemented by home exercise guidelines is effective in improving the exercise capacity of cardiac patients.
Table 1. Patient demographics and medications

<table>
<thead>
<tr>
<th>Patients n (M:F)</th>
<th>41 (38:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>n (%)</th>
<th>Medications</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>31 (76%)</td>
<td>ASA</td>
<td>35 (85%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>6 (15%)</td>
<td>Beta Blocker</td>
<td>32 (78%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>11 (27%)</td>
<td>Ace Inhibitor</td>
<td>27 (66%)</td>
</tr>
<tr>
<td>Angina</td>
<td>1 (2%)</td>
<td>Antiplatelet</td>
<td>27 (66%)</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>9 (22%)</td>
<td>Statin</td>
<td>31 (76%)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>3 (7%)</td>
<td>Ca Channel Blocker</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Wolf-Parkinson-White</td>
<td>1 (2%)</td>
<td>ARB</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (2%)</td>
<td>Broncho Dilator</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>19 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>10 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic Valve Repair</td>
<td>8 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral Valve Repair</td>
<td>2 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid Valve Repair</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td>2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>3 (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>14 (34%)</td>
<td></td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>12 (29%)</td>
<td></td>
</tr>
<tr>
<td>History of Dyslipidemia</td>
<td>11 (27%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>9 (22%)</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>6 (15%)</td>
<td></td>
</tr>
<tr>
<td>Renal Failure</td>
<td>4 (10%)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

STEMI, ST elevated myocardial infarct; NSTEMI, non-ST elevated myocardial infarct; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft; PVD, peripheral vascular disease; ASA, acetylsalicylic acid; ARB, angiotensin II receptor blocker
QIQC-CLIN-2

ASSESSING THE HEART TEAM APPROACH IN OPTIMIZING CORONARY REVASCULARIZATION

Mohammad Almutawa, Jay Shavadia, Kevin Bainey, Seraj Abualnaja, Steven Meyer, Chai Paterson, Wayne Tymchak, Robert Welsh

Background: Following the SYNTAX trial, the multidisciplinary team (MDT) strategy has emerged as the optimal approach in determining best treatment for patients with multivessel coronary artery disease (CAD). At our institution, interventional cardiologists meet weekly to assess and propose best treatment (coronary artery bypass surgery [CABG], percutaneous coronary intervention [PCI], conservative management) for the patients with complex multivessel CAD (PCI Meeting). Subsequently, cardiac surgeons, cardiologists, interventional cardiologists and other allied healthcare professionals meet in a similar fashion (weekly) to discuss optimal treatment in a MDT meeting format. We aim to examine treatment allocation and clinical outcomes of PCI and MDT meetings in approaching complex coronary artery disease.

Methods: Data were collected retrospectively from the PCI and MDT meeting registry, APPROACH cardiac catheterization reports and patients' medical records between July 2014 and April 2015. Patients were divided into 4 groups based on the proposed therapy from the PCI meeting; medical therapy (group 1), CABG (group 2), PCI (group 3) or either PCI or CABG (group 4). Subsequent therapy following MDT recommendations were compared with the primary outcome defined as whether patients received the therapy proposed at the initial PCI meeting. The secondary outcome was a composite of death, cerebrovascular accident (CVA), myocardial infarction (MI) or acute renal failure (ARF) at 30 days.

Results: The number of patients reviewed at the PCI and MDT meetings included 119 during the 8 months period. Only clinically stable patients were reviewed at these meetings of which 82.4% were male and 39.5% had diabetes mellitus. Left anterior descending artery (LAD) involvement was observed in 73.1%, three vessel CAD documented in 11.8%, and 11.8% had left main stem (LMS) lesions. A total of 12.0% of patients had severe LV dysfunction of EF <30%. For the primary outcome, actual treatment received is illustrated in (Fig 1). In Group 1 (medical therapy [n=25]) 96.0% received medical therapy. Group 2 (CABG [n=47]), 87.0% received CABG. Group 3 (PCI [n=37]) 79.0% had received PCI. In Group 4 (PCI or CABG [n=14]) 57.1% received CABG, 35.7% received PCI, and 7.0% had medical therapy. The secondary composite outcome occurred in 17 patients; 5 following PCI (4.2%), 8 following CABG (6.7%), and 4 with medical therapy only (3.4%). Conclusion: The interventional cardiology PCI meeting correlated well with recommendations provided following MDT discussion. Differences in clinical outcomes were noted at 30 days. Whether PCI and/or MDT meetings mitigate patients risk remains to be determined.
Figure 1
**QIQC-CLIN-3**

**DO CANADIAN TEACHING HOSPITAL CCUS HAVE BETTER PATIENT OUTCOMES THAN COMMUNITY HOSPITALS? DATA ON 73,338 PATIENTS WITH ACUTE CORONARY SYNDROMES OR HEART FAILURE ADMITTED TO CCUS**

Sanam Verma, Padma Kaul, Meng Lin, Justin A. Ezekowitz, David A Zygun, Finlay A. McAlister, Sean van Diepen

**Background:** Acute coronary syndromes (ACS) and heart failure (HF) are the leading diagnoses in patients admitted to coronary care units (CCU). However, it is unknown whether resource utilization and outcomes vary between hospital types – including size and community or teaching focus. We evaluated rates of CCU admission, CCU therapies, and clinical outcomes across Canadian hospitals.

**Methods:** Canadian Institute for Health Information data was used to identify patients aged ≥ 18 years hospitalized in with a primary diagnosis of an ACS (ST-segment elevation myocardial infarction [STEMI], non STEMI [NSTEMI], unstable angina [UA]) or HF in 9 Canadian provinces between April 1, 2007 and March 31, 2013. CCUs were categorized by hospital type as follows: teaching (any size), large (≥200 beds), medium (50-199 beds), and small (1-49 beds) community hospitals. We examined CCU admission rates, and critical care therapy/procedure use. The outcomes of interest were in-hospital mortality and 30-day post-discharge all-cause readmission among patients admitted to CCUs.

**Results:** Among the 220,759 hospitalized patients, 73,338 (33.2%) were admitted to a CCU. The proportion of patients admitted to a CCU varied across hospital types: 20,963 (41.0%) in teaching, 31,110 (29.9%) in large, 18,125 (42.6%) in medium, and 3,140 (13.7%) in small community hospitals. The percentage of patients that received critical care therapies in teaching, large, medium and small hospitals were 73.6%, 50.9%, 24.6%, and 8.8% (p<0.0001), respectively. Compared to patients admitted to CCUs in teaching hospitals, patients admitted to CCUs in community hospitals had higher in-hospital mortality rates (Table). Similar findings were observed for 30-day all-cause readmission in patients with STEMI and NSTEMI, but not in patients with UA or HF.

**Conclusion:** Patients admitted with ACS or HF to teaching hospital CCUs had a higher use of CCU therapies, and lower adjusted mortality and 30-day re-admission rates compared to community hospitals. These differences highlight differences and potential disparities in CCU admission practices, resource utilization, and outcomes across hospitals types in Canada.
### TABLE: In-hospital mortality and 30-day readmission rates of patients hospitalized acute coronary syndromes or heart failure to coronary care units by hospital type in Canada

<table>
<thead>
<tr>
<th>In-hospital Mortality</th>
<th>Teaching (n=20,963)</th>
<th>Large Community (n=31,110)</th>
<th>Medium Community (n=18,125)</th>
<th>Small Community (n=3,140)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>aOR (95% CI)</td>
<td>%</td>
<td>aOR (95% CI)</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>7.6</td>
<td>10.1 1.41 (1.13, 1.76)</td>
<td>9.8</td>
<td>1.33 (1.09, 1.62)</td>
</tr>
<tr>
<td><strong>All ACS</strong></td>
<td>6.3</td>
<td>9.8 1.61 (1.27, 2.03)</td>
<td>8.8</td>
<td>1.55 (1.24, 1.94)</td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
<td>7.8</td>
<td>13.1 1.82 (1.35, 2.45)</td>
<td>15.7</td>
<td>1.98 (1.34, 2.71)</td>
</tr>
<tr>
<td><strong>NSTEMI</strong></td>
<td>5.8</td>
<td>7.3 1.46 (1.10, 1.94)</td>
<td>7.8</td>
<td>1.40 (1.05, 1.86)</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
<td>0.8</td>
<td>0.6 0.89 (0.39, 2.07)</td>
<td>0.4</td>
<td>0.50 (0.20, 1.27)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>25.4</td>
<td>21.6 0.90 (0.69, 1.17)</td>
<td>17.2</td>
<td>0.83 (0.63, 1.09)</td>
</tr>
<tr>
<td><strong>30-day readmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>7.2</td>
<td>11.1 1.24 (1.08, 1.41)</td>
<td>13.1</td>
<td>1.31 (1.13, 1.51)</td>
</tr>
<tr>
<td><strong>All ACS</strong></td>
<td>7.4</td>
<td>11.6 1.30 (1.12, 1.52)</td>
<td>13.5</td>
<td>1.35 (1.14, 1.61)</td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
<td>6.7</td>
<td>10.5 1.26 (1.05, 1.50)</td>
<td>12.7</td>
<td>1.29 (0.97, 1.71)</td>
</tr>
<tr>
<td><strong>NSTEMI</strong></td>
<td>8.1</td>
<td>13.0 1.39 (1.14, 1.65)</td>
<td>14.8</td>
<td>1.44 (1.21, 1.72)</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
<td>8.5</td>
<td>9.8 1.10 (0.89, 1.36)</td>
<td>11.8</td>
<td>1.23 (1.02, 1.54)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>9.8</td>
<td>11.5 1.09 (0.90, 1.32)</td>
<td>12.4</td>
<td>1.17 (0.95, 1.43)</td>
</tr>
</tbody>
</table>

* Unadjusted outcome percentage;

Abbreviations: aOR, adjusted Odds Ratio; adjusted for baseline demographics, co-morbidities, in-hospital critical care therapies, percutaneous coronary intervention, coronary artery bypass, resource intensive weighting, and province.
QIQC-CLIN-4

VARIATION IN TIME TO DISPOSITION IN THE EMERGENCY DEPARTMENT FOR PATIENTS WITH SUSPECTED ACUTE CARDIOVASCULAR DISEASE: INSIGHTS FROM PROACT-3 AND 4 TRIALS


Background: The Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROACT) 3 and 4 trials were designed to test the role of pre-hospital biomarker testing in reducing time to disposition from the emergency department (ED) in patients with symptoms of acute cardiovascular disease. A variation in time in the ED (the primary endpoint) between sites was noted. In this analysis, we compared the time and patient outcomes between the hospitals of PROACT-3 and 4 trials and explored the potential patient- and hospital-related factors.

Methods: The cohorts of PROACT-3 and 4 trials were pooled (n=1,076 patients). Time from first medical contact to disposition from ED (primary endpoint) and its components were compared between the 5 EDs. 30-day death, repeat ED visits, and re-hospitalizations were evaluated. GRACE risk score was used for risk adjustment. The troponin testing pattern (point of care troponin, first and second in-ED troponin) was compared between EDs.

Results: Baseline characteristics, cardiovascular risk and ED diagnosis were similar between patients from different participating EDs. There was variation in primary endpoint as patients from ED-5 had a shorter time to disposition from ED compared to other EDs (7.40 vs 9.15 hours, p<0.001). A higher rate of patients from ED-5 were discharged directly from ED (p<0.001). This earlier disposition from ED was not associated with a higher clinical event rate for 30-day all-cause death, repeat ED visit and re-hospitalization (all p>0.05). Patients from ED-5 had a lower rate of elevated troponin >0.1 ug/L results (5.5% vs 17.4%, p=0.001) and fewer number of second troponin tests done at ED (Table 1).

Conclusion: There was considerable site variation in time from first medical contact to disposition from ED in patients within the PROACT-3 and 4 trials despite similar CV risk and demographics. This ED variation may have been driven by fewer elevated and second troponin tests but differences in process of care may also be responsible. Further assessment of site based variation with sensible rapid triage and accelerated troponin testing for patients with CV symptoms should facilitate timely discharge and health resource utilization.
Table 1: Baseline characteristics, primary endpoint and clinical outcomes between participating trial sites

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>ED 1</th>
<th>ED 2</th>
<th>ED 3</th>
<th>ED 4</th>
<th>ED 5</th>
<th>p-value</th>
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<tbody>
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<td>1076</td>
<td>360</td>
<td>350</td>
<td>120</td>
<td>137</td>
<td>109</td>
<td>0.144</td>
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<tr>
<td>Age, years</td>
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<tr>
<td></td>
<td>68 (54, 80)</td>
<td>68 (56, 79)</td>
<td>65 (53, 78)</td>
<td>69 (54, 80)</td>
<td>71 (54, 82)</td>
<td>70 (55, 80)</td>
<td>0.144</td>
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<tr>
<td>Female, %</td>
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<td></td>
<td>47</td>
<td>48</td>
<td>41</td>
<td>50</td>
<td>54</td>
<td>50</td>
<td>0.078</td>
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<td>GRACE risk score</td>
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<tr>
<td></td>
<td>114 (87, 142)</td>
<td>115 (93, 144)</td>
<td>109 (85, 139)</td>
<td>118 (86, 143)</td>
<td>120 (90, 148)</td>
<td>113 (85, 136)</td>
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<tr>
<td>Diabetes, %</td>
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<td>27</td>
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<td>Prior PCI, %</td>
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<td></td>
<td>17</td>
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<td>21</td>
<td>16</td>
<td>11</td>
<td>14</td>
<td>0.061</td>
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<tr>
<td>Prior HF, %</td>
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<td>10</td>
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<td>13</td>
<td>10</td>
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<td>0.406</td>
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<td>Direct ED discharge, %</td>
<td>71</td>
<td>67</td>
<td>67</td>
<td>74</td>
<td>75</td>
<td>85</td>
<td>0.001</td>
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<tr>
<td><strong>Timing variables</strong></td>
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<td></td>
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<tr>
<td>First medical contact to final disposition, h</td>
<td>9.02 (6.53, 11.16)</td>
<td>9.52 (7.47, 11.64)</td>
<td>8.87 (6.58, 10.62)</td>
<td>9.97 (6.93, 13.17)</td>
<td>8.58 (5.58, 11.40)</td>
<td>7.40 (5.53, 9.12)</td>
<td>&lt;0.001</td>
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<tr>
<td>Triage to ED discharge, hours</td>
<td>8.15 (5.65, 10.20)</td>
<td>8.70 (6.48, 10.62)</td>
<td>8.11 (5.85, 9.70)</td>
<td>9.03 (6.01, 12.32)</td>
<td>7.51 (4.34, 10.61)</td>
<td>6.35 (4.70, 8.15)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>30-day outcomes, %</strong></td>
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<tr>
<td>All-cause death</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0.602</td>
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<tr>
<td>Repeat ED visit</td>
<td>14</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>0.281</td>
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<tr>
<td>Re-hospitalization</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>0.681</td>
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**Troponin testing, %**

<table>
<thead>
<tr>
<th></th>
<th>Pre-hospital POC- troponin</th>
<th>First ED Troponin T1</th>
<th>Second ED Troponin T2</th>
<th>ED Troponin &gt;0.1</th>
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<tr>
<td></td>
<td>41</td>
<td>96</td>
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<td>38</td>
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<td>19</td>
<td>21</td>
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<td></td>
<td>45</td>
<td>97</td>
<td>18</td>
<td>20</td>
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<td></td>
<td>40</td>
<td>98</td>
<td>22</td>
<td>10</td>
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<td></td>
<td>39</td>
<td>91</td>
<td>14</td>
<td>16</td>
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<tr>
<td></td>
<td>45</td>
<td>97</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Data are median (IQR), or %. ED: emergency department; POC: point-of-care
TEMPORAL TRENDS AND PREDICTORS OF HOSPITALIZATION AND LENGTH OF STAY OF VENOUS THROMBOEMBOLISM IN ALBERTA FROM 2002 TO 2012

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

Background: Venous thromboembolism (VTE) causes significant risk of morbidity and mortality as well as substantial medical costs. Recent studies emphasize the importance of outpatient care for low-risk VTE, starting from the advent of the low molecular weight heparin.

Aims: The aim of this study is to describe the temporal changes in the hospitalization rates and length of stay of VTE over a 10-year period in the province of Alberta. We described the rates of hospitalization, length of stay and compared patient demographics and comorbidities among hospitalized and non-hospitalized patients.

Methods: Using linked administrative health databases in the province of Alberta, we identified all patients with a primary diagnosis of VTE between April 2002 and March 2012. The cohort included adult patients with any health care encounter coded as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) using a validated case-defining criteria. We used multivariate linear and logistic regressions to model outcomes.

Results: During the study period, 8,198 out of 31,656 VTE cases were hospitalized. The overall rate of hospitalization was 52.0% for PE and 16.1% for DVT patients. The rate of hospitalization fluctuated between 27.8% and 23.7% with no evident temporal trend (p=0.10). Also, the length of stay remained unchanged during this period with a median (IQR) of 7 (4-11) days (p=0.67) (Table and Figure 1). Higher Charlson comorbidity index, older age, pulmonary embolism at presentation and male gender increased the odds of hospitalization.

Conclusion: The study showed that there were no significant changes in hospitalization or length of stay for VTE over the last decade. Also, patients presenting with PE and multiple comorbidities tend to get hospitalized and stay longer.
### Table 1: Secular Trends for Length of Stay of Albertan Hospitalized for Venous Thromboembolism by Year from 2004-2012

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of hospitalized patients (%)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>1037(27.8)</td>
<td>11.0(14.11)</td>
<td>7 (4-12)</td>
</tr>
<tr>
<td>2006</td>
<td>1066(27.8)</td>
<td>10.3(13.4)</td>
<td>6 (4-11)</td>
</tr>
<tr>
<td>2007</td>
<td>994(27.5)</td>
<td>10.7(18.5)</td>
<td>7 (4-11)</td>
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<tr>
<td>2008</td>
<td>961(24.7)</td>
<td>11.3(17.6)</td>
<td>7 (4-11)</td>
</tr>
<tr>
<td>2009</td>
<td>942(23.7)</td>
<td>11.3(15.9)</td>
<td>7 (4-12)</td>
</tr>
<tr>
<td>2010</td>
<td>1013(24.4)</td>
<td>10.6(16.8)</td>
<td>7 (4-11)</td>
</tr>
<tr>
<td>2011</td>
<td>1064(26.0)</td>
<td>11.0(18.1)</td>
<td>7 (4-11)</td>
</tr>
<tr>
<td>2012</td>
<td>1121(25.7)</td>
<td>11.0(18.8)</td>
<td>6 (3-11)</td>
</tr>
<tr>
<td>Total</td>
<td>8198(25.9)</td>
<td>10.9(16.8)</td>
<td>7 (4-11)</td>
</tr>
</tbody>
</table>
LACK OF CHANGE IN ARTERIAL STIFFNESS AND VASCULAR FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS ADMITTED TO HOSPITAL

Wade Michaelchuk, Irene J. Andersson, Desi P. Fuhr, Mohit Bhutani, Ron Damant, Brian Rowe, Richard Leigh, Michael Stickland

Background: Chronic obstructive pulmonary disease (COPD) is associated with substantial cardiovascular (CV) morbidity/mortality. This is further increased when patients experience an Acute Exacerbation of COPD (AECOPD). Both arterial stiffness and endothelial dysfunction are predictive of CV risk, and both are elevated in COPD. The purpose of this study is to evaluate the effect of an AECOPD on arterial stiffness and vascular function in COPD patients enrolled in the COMMAND (Placebo Controlled Study of VS-6063 in Subjects with Malignant Pleural Mesothelioma) study.

Methods: Patients admitted to the University of Alberta Hospital for an AECOPD were screened (n=686) and recruited (n=81, age=68 ± 8, FEV1=34.0 ± 15.5% predicted) within the Emergency Department. Arterial stiffness, assessed by carotid radial pulse wave velocity (Complior Analyse), and endothelial function, assessed by reactive hyperemia index (RHI, Endo-PAT2000), were used to evaluate CV function within 24 hours of admission, at discharge, and 14 days after discharge.

Results: No significant change in arterial stiffness was detected during the hospitalization for AECOPD or at 14 days post discharge (Admission: 8.9 ± 3.6 m/s; Discharge: 10.4 ± 5.2 m/s; 14 Day Follow-up: 8.6 ± 2.4 m/s; p>0.05). Arterial stiffness measured in hospital was similar to previously published work in stable COPD patients. COPD patients demonstrated normal endothelial function (RHI > 1.67) at admission and 14 day follow-up and did not show significant changes while in hospital or at home (Admission: 1.73 ± 0.38; Discharge: 1.88 ± 0.51; 14 Day Follow-up: 1.81 ± 0.54; p>0.05).

Conclusion: Preliminary results indicate that an AECOPD hospitalization does not alter CV function/risk. Further, neither arterial stiffness nor vascular function improve once the patient has returned home.
ACOUSTIC DIAGNOSIS OF PULMONARY HYPERTENSION: AUTOMATED SPEECH-RECOGNITION-INSPIRED CLASSIFICATION ALGORITHM OUTPERFORMED CARDIOLOGISTS.

Tarek Kaddoura, Prashant Bobhate, Shine Kumar, Long Guo, Shreepal Jain, Mohamed Elgendi, Karun Vadlamudi, James Coe, Daniel Kim, Dylan Taylor, Wayne Tymchuk, Dale Schuurmans, Roger Zemp, Ian Adatia

Background: The diagnosis of pulmonary hypertension (PH) is delayed or missed during the early stages of the disease because the clinical signs are difficult to discern. We sought to investigate whether speech recognition algorithms could differentiate between the pulmonary heart sounds (P2) in subjects with and without PH. Furthermore, we hypothesized that an automated, speech-recognition-inspired classification algorithm applied to heart sound recordings would outperform trained clinicians in the diagnosis of PH.

Methods: Heart sounds, electrocardiograms, and pulmonary artery pressures (PAP) were recorded simultaneously. Digitized heart sound recordings were used to train and test speech-recognition-inspired classification algorithms. We extracted heart sound features with Mel-Frequency Cepstral Coefficients. We built Gaussian-Mixture Models to classify the features as PH or non-PH. Clinicians, blinded to clinical data, listened to randomized digitized phonocardiograms. We defined PH as a mean PAP ≥25 mmHg.

Results: We studied 164 subjects, 86 with PH (median age 41 years (0.3-84), 45 females, mean PAP 41±13 mmHg) and 78 without PH (median age 17 years (0.6-86), 41 females, mean PAP 17 ± 4 mmHg.) The automated speech-recognition-inspired algorithm diagnosed PH with a true positive rate of 74% (area under the receiver-operating-characteristic curve of 0.74), false negative rate of 23%, false positive rate of 34%. Clinicians diagnosed PH from the heart sound recordings with a true positive rate of 56%, false negative rate 68% and false positive rate of 50% (p < 0.05).

Conclusion: We found that digital auscultation with the application of automated speech-recognition-inspired classification algorithms to recorded heart sounds results in a 74% correct diagnosis of PH and performed significantly better than clinicians listening to the same heart sound recordings. Our results suggest that changes in P2 are related directly to an increased PAP and that computer-aided diagnosis could be used as a screening tool in the early diagnosis of PH.
QUALITY OF LIFE AND FRAILTY FOLLOWING TRANSCATHETER AORTIC VALVE IMPLANTATION

Chai Paterson, Pishoy Gouda, Steve Meyer, Miriam Shanks, Craig Butler, Dylan Taylor, Ben Tyrrell, Robert Welsh, Robert Welsh

Background: Transcatheter aortic valve implantation (TAVI) is an established alternative to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis and increased surgical risk. Frailty is a critical clinical metric that heart teams assess to select TAVI over SAVR. To date there has been limited data assessing frailty assessed sequentially over time in TAVI patients and the relationship of frailty to quality of life measurements.

Methods/Results: From June 2012 to June 2015, 159 consecutive patients underwent TAVI. Of these, 65 had undergone sequential frailty testing and completed quality of life questionnaires pre-TAVI and one-month post-TAVI. In this cohort, the mean age was 85.5 +/- 6.25 years, 56.9% were male and mean body mass index was 27.8 +/- 5.0. Mean baseline ejection fraction (EF) was 55.4% +/- 10.3 and mean post-TAVI EF was 57.9% +/- 6.8. At baseline participants reported an activities of daily living disability mean score of 3.22 +/- 2.1, with a mean improvement of 1.0 +/- 2.5 at one month. Participants scored their overall baseline wellbeing at a mean of 58.8% +/- 19.2, which increased to 71.4% +/- 14.8 at one month. Using the Minnesota Quality of Life questionnaire, patients reported a baseline mean score of 52.3% +/- 23.0 for physical components and 13.0% +/- 18.4 for emotional components, which improved to 21.2% +/- 18.8 and 2.6% +/- 6.0 respectively. Frailty measured by hand grip strength did not improve with a mean of 24.5 +/- 7.8 at baseline which decreased to 23.7 +/- 7.3 at one month. The walk test had modest improvement with 50.0% passing the walk test at baseline 50.0% and 55.6% at one month.

Conclusion: Consistent with known data, patients who have undergone TAVI report consistent improvements in quality of life one-month post-TAVI using a variety of instruments to evaluate quality of life. However, measurement of frailty using handgrip and walk test as a surrogate for frailty had no significant short-term improvements in frailty. Understanding frailty and its impact on patient selection and outcomes is critical and warrants further consideration.
NURSING POSTERS
CHD-NUR-1

TEENS WITH CONGENITAL HEART DISEASE IN TRANSITION FROM PEDIATRIC TO ADULT CARE: QUALITATIVE EVALUATION OF NURSE-LED INTERVENTION TO SUPPORT TRANSITION READINESS

Steffany Charles, Gwen R. Rempel, Laura G. Rogers, Kathryn Rankin, Elina Williams, Michelle Schuh, Dimi Dragieva, Sonila Mustafa, Samantha Anthony, Ahlexxi Jelen, Miriam Kaufman, Adrienne H. Kovacs, Brian McCrindle, David Nicholas, Erwin Oechslin, Renee Sananes, Andrew S. Mackie

Background: Adolescent survivors of congenital heart disease (CHD) require lifelong specialized health care. Effective transition programs from pediatric to adult-care are warranted, but outcome data remain limited. The Congenital Heart Adolescents Participating in Transition Evaluation Research (CHAPTER 2) Study is a two-center randomized controlled trial of a nurse-led transition intervention. We sought to describe qualitative data from this trial.

Methods: Adolescents aged 16-17 years with moderate or complex CHD were cluster randomized to a transition intervention or usual care. The two-session intervention was conducted by one of five registered nurses in Edmonton and Toronto. Session 1 (1 hour) emphasized patient education and included creation of a MyHealth Passport and goal setting. Session 2 (1.5 hours), two months later, emphasized self-management skill development. It included a follow-up on goal setting, viewing videos on doctor-patient interactions, and participating in role-play scenarios. Qualitative data extracted from intervention logs, study nurses’ field notes, and audio recordings of the sessions were analyzed for content and themes.

Results: Data from 111 sessions with 57 adolescents were analyzed. Creation of the MyHealth Passport, goal setting and role-plays were the most valued steps for participants. Most participants set goals with minimum prompting (79%), and by Session 2, 62% reported working on their goal. Most engaged in role play with minimal prompting (73%). The majority reported keeping their passport on their person when outside the home (78%). Analysis of participants in the intervention group revealed 4 categories: 1) the independent adolescent who was already managing aspects of their own care prior to the intervention (5%); 2) the adolescent who was ready for transfer after completing both sessions (46%); 3) the “at-risk” adolescent who engaged in risky behaviours and appeared uninterested in learning how to manage their own health (14%); and, 4) the adolescent who was in need of further sessions; they did not have a good understanding of their CHD, struggled with goal setting, and lacked confidence in the role-play scenarios (26%). Nine percent of adolescents could not be classified based on the qualitative data available.

Conclusion: Qualitative analysis of extensive data generated in this clinical trial contributed to determining the most important components of the nurse-led sessions: creation of a MyHealth passport, goal-setting, and role-plays. Forty percent of the adolescents required further intervention after the two sessions, suggesting that transition interventions should begin earlier in adolescence. An individualized approach based on an assessment of transition readiness is warranted.
QIQC-NUR-1
MORAL DISTRESS AND BURNOUT AMONG HEALTHCARE PROVIDERS IN A CARDIOVASCULAR INTENSIVE CARE
Sean M Bagshaw, Mandy Bellows, Jasdip Dhaliwal, Leah Johnson-Coyle, Sydney Richardson-Carr, Dawn Opgenorth

Background: The intensive care unit (ICU) is a busy, high stress, complex environment. The cardiovascular ICU (CVICU) at the Mazankowski Alberta Heart Institute (Maz) has recently been characterized by high acuity and complexity, strained occupancy and challenging end-of-life care, raising concern health care providers are experiencing high levels of moral distress and burnout. An inter-professional team aimed to describe the prevalence and contributing factors to moral distress and burnout among all CVICU providers.

Methods: Web-based survey of providers (registered nurses [RN]/nurse practitioners [NP]; registered respiratory therapists [RRT]; allied health and physicians) working in a 24-bed CVICU at the Maz between June 15–29, 2015. The survey captured demographic data and integrated the Moral Distress Scale-Revised and the Maslach Burnout Inventory™ instruments.

Results: One hundred sixty-nine providers completed the survey (response rate 88%). Moral distress was higher among RN/NPs (median [IQR] MDS-R score 80 [57-110]) and RRTs (85 [61-104]) compared with allied health (54 [39-66]) and physicians (66 [43-82], p=0.06). The highest ranking sources of moral distress across all providers were: “Continue to participate in the care for a hopelessly ill person who is being sustained on a ventilator, when no one will make a decision to withdrawal support”; “follow a family’s wishes to continue life support even though I believe it is not in the best interest of the patient” and “witness healthcare providers giving “false hope” to a patient or family”. Emotional exhaustion and depersonalization were more prevalent in RN/NPs (moderate-to-high: 70%; 69%) and RRTs (moderate-to-high: 80%; 80%), while high personal accomplishment was lowest (30%; 20%), when compared with allied health and physicians. Moral distress was positively correlated with emotional exhaustion (r = 0.41; p<0.01) and depersonalization (r = 0.27; p<0.01) and negatively correlated with workplace satisfaction, specifically with the perception of “recognition for good work” (r = -0.26; p<0.01) and “attention paid to suggestions” (r = -0.29; p<0.01).

Conclusion: Moral distress and burnout are common across inter-professional providers in the CVICU; and most prevalent among nurses and RRTs. Five themes emerged as contributing factors including: care of complex patients, team communication, provision of non-beneficial therapy, end-of-life-care and strained capacity. These findings will direct the development of strategies to mitigate and manage moral distress and burnout among inter-professional CVICU providers.
QIQC-NUR-2

PATIENT EXPERIENCE: A UNIT LEVEL UNDERSTANDING

Mandy Bellows, Mishaela Houle

Background: Alberta Health Services (AHS) is patient focused and provides aggregate zone and site level patient satisfaction data to support system improvement. The Edmonton Zone Cardiac Sciences Program sought to understand patient and family experiences at the unit level; bringing awareness to patient concerns, suggestions and satisfaction rates to facilitate contextual quality improvement. To date, this is the first AHS program wide unit level patient satisfaction initiative.

Methods: In September 2014, a draft in-patient satisfaction card was developed based on literature from Picker Institute Europe, Institute for Patient and Family Centered Care, Institute for Healthcare Improvement, Hospital Consumer Assessment of Health Providers and Systems, Canadian Institute for Health Information, and AHS Patient Experience Department. The card was piloted on the Cardiology Unit at the Mazankowski Alberta Heart Institute (Maz) in November and December 2014. Feedback from patients, families and staff were incorporated to improve the card (i.e. format, language) and the process for its delivery and completion. The cards include quantitative likert-style questions pertaining to: Communication, Nurse & Clinician Responsiveness, Physical Environment, Medication & Pain Control, Care Coordination, People Centred Care and overall experience satisfaction. Additionally, the cards offer space for patients and family members to provide qualitative responses and their contact details if involvement in future quality improvement activities is desired.

Results: AHS defines patient satisfaction based on the percentage of 8, 9 and 10 responses on a scale from 1 (bad) to 10 (excellent). The overall in-patient satisfaction rate for the Cardiac Sciences Program was 92% in 2014/2015; and 93% in 2015/2016. For the majority of cases, in the areas of Communication, Nurse & Clinician Responsiveness, Physical Environment, Medication & Pain Control, Care Coordination, People Centred Care respondents selected “always” versus “usually”, “hardly” or “never”.

Conclusion: Supporting unit level quality and patient safety improvement initiatives with insights from patients and families is vital. The data helps target quality improvement efforts and acknowledge healthcare providers. Patient responses are shared with healthcare providers to support learning and staff engagement. Due to pilot success, the in-patient satisfaction card was rolled out to all in-patient units throughout the Edmonton Zone Cardiac Sciences Program, and was revised to fit the context of Ambulatory Care Clinics, Cardiac Recovery Rooms, and the Northern Alberta Cardiac Rehabilitation Program. Receiving patient and family perspectives from the point-of-care assists healthcare providers and administrators to address any concerns or changes in the care experience in a timely manner.
Background: Due to the lack of standards or guidelines regarding the number of acceptable peripheral Intravenous (PIV) site infections, the Mazankowski Alberta Heart Institute Cardiology unit identified an opportunity for improvement. To build awareness on PIV site infections and understand the current rate of PIV site infections the cardiology unit began tracking PIV and identified five incidents of PIV site infections between April 22nd and July 16th 2015. These PIV site infections resulted in procedure cancellations, peripherally inserted central catheter line insertions for long-term intravenous antibiotics treatments, an increased length of stay, and inevitably complicating patient hospitalization and producing a poor patient experience. This triggered the Cardiology Unit Quality Council of frontline staff to embark on an improvement opportunity. An investigation into root cause analysis was conducted.

Methods: The Cardiology Unit Quality Council followed the Plan-Do-Study-Act methodology in the investigation for the cause for the PIV site infections. Baseline data was collected and displayed on the Unit quality board including: Date of infection/insertion, hours PIV was in place, facility PIV inserted, if insertion was completed as per policy, treatment and patient outcome/impact. Data was collected and collated from July-September of 2015. An increased awareness of PIV best practice and documentation was highlighted and reinforced by the frontline staff, the use of IV insertion trays was discontinued, all non compliant IV site dressings were reported and highlighted, and assessment documentation of PIV sites augmented.

Results: Several opportunities for improvement were identified within the program. Due to the raised awareness of the impact a PIV site infection can have on a patient and multiple changes made by the cardiology unit there have been no PIV site infection’s since July 16, 2015 to April 7, 2016. This is a reduction in hospital length of stay, an improved patient outcome and experience, as well as significant cost savings.

Conclusion: Through the innovative and collaborative efforts of key frontline individuals committed to best practice and facilitated by the Cardiology Unit Quality Council at the Mazankowski Alberta Heart Institute achieved its goal of decreasing PIV site infections. A culture dedicated to patient and family centered care will enable us to continue our efforts toward maintaining 0% PIV site infections.
COLLABORATIVELY IMPROVING CARDIOLOGY IN-PATIENT FLOW

Lisa Marco, Kimberly Simpson, Miriam Shanks, Stacy Krenkel, James Simon, Mandy Bellows

Background: In 2015, the Mazankowski Alberta Heart Institute (Maz) Cardiology Unit initiated a review of the daily activities of patient flow. The Multidisciplinary Cardiology Unit Quality Council determined that the actual length of patient stay was greater than the estimated length of patient stay (ALOS/ELOS). Factors contributing to this include unclear roles and responsibilities for daily rounds and breakdowns in communication pertaining to the early identification and barriers to discharge. The purpose of this quality improvement initiative was to develop a standard for daily rounding, enhance communication and increase efficiency surrounding patient discharge from hospital.

Methods: Utilizing the Plan-Do-Study-Act methodology, the improvement initiative involved two stages; one starting in July 2015 and the other in November 2015. The first stage focused on the daily bedside rounding process and the second on the discharge process. Five target objectives were identified: bedside nurse present at daily rounds; appropriate information available; increase number of discharges between 0700-1400; decrease patient length of stay; and improve the ALOS/ELOS. Collaboratively, the team developed a standard for daily patient rounds by process mapping the patient journey from admission to discharge. This included: defining team roles, rescheduling rapid rounds to eliminate rounds interruptions, defining information standard required during daily rounds and implementing effective communication tools for healthcare providers. Stage two involved the implementation of a dedicated discharge section in the chart, a discharge checklist, standardized social assessment on admission, and enhanced communication processes during discharge planning.

Results: Table 1 provides an overview of the target objectives. As a result of this initiative, there was an increase in bedside nurse presence at daily rounds, increased number of discharges between 0700-1400, and appropriate information available during rounds, and a decrease in ALOS/ELOS. Developing a standard for daily patient rounds and discharge led to a decrease of 5.0 to 4.5 days (9.3%) in hospital length of stay over 12 months; potentially resulting in significant cost savings.

Conclusion: Through innovative collaborative efforts the cardiology program at the Maz achieved its target of increasing the effectiveness of daily rounds, enhancing communication and reducing hospital length of stay by 9.3% when comparing 2014/2015 fiscal year (FY) and 2015/2016 FY. Involvement from multiple stakeholders of the Cardiology Program including physicians, a nurse practitioner, pharmacists, bedside nurses, and management supported successful implementation of quality improvement efforts resulting in decreased hospital length of stay and enhanced patient and family experience.
QIQC-NUR-5

HEART FAILURE: A COLLABORATIVE SELF-CARE APPROACH

Melissa Perri, Mandy Bellows

**Background:** There has been a shift in focus of who is responsible for a patient’s health. This shift is caused by the increasing amount of self-care that is used to manage a patient’s condition. Increasing demand on the system, due to a high number of patients with chronic conditions and the complexity of these conditions is building a case for patient self-care management. A transition towards self-care is needed as treatment goals for chronic conditions include long-term management, as care cannot stop once the patient leaves hospital.

**Methods:** Orem’s Self Care Deficit theory is examined and applied to heart failure treatment in the acute care setting as seen through the lens of a critical care nurse.

**Results:** Using self-care as a tool to manage heart failure increases the patient’s ability to approach their care with increased knowledge and access to community resources. Orem’s self-care deficit theory and the “traffic light” system allow nurses to build supportive relationships with patients while sustaining a responsive healthcare system. An interdependent approach to healthcare can decrease heart failure complications, prevent emergency room visits and hospital readmissions.

**Conclusion:** When examining how self-care can be implemented in chronic disease management the concepts of autonomy and independence require exploration. By exploring the relationship between the healthcare professional and patient, it is determined that the patient does not act independently when managing their chronic condition. Instead, the healthcare professional and patient have an interdependent relationship and are both responsible for the patient’s chronic condition management.
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:

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
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:

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 Ezekowtiz
2005 - Dr. Michael McDonald
2004 - Dr. Michael McDonald
2003 - Dr. Taha Taher
2002 - Dr. Raymond Leung
2001 - Dr. Bernard Thebaud & Dr. Bernardo V. Alvarez
Dr. Francis X. Witkowski Award

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

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

PAST AWARD WINNERS:

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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