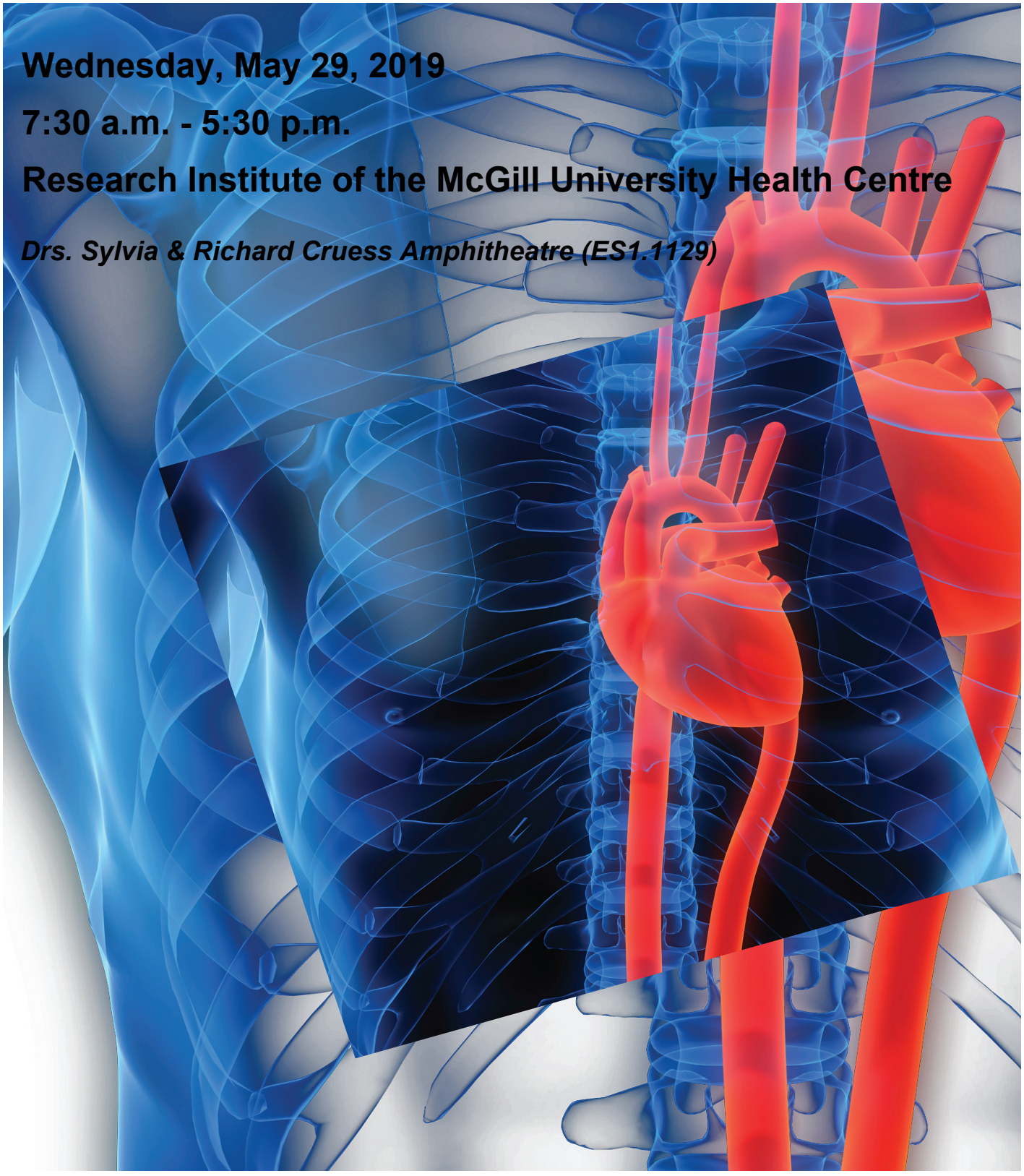
McGILL CARDIOVASCULAR RESEARCH DAY



Wednesday, May 29, 2019

7:30 a.m. - 5:30 p.m.

Research Institute of the McGill University Health Centre

Drs. Sylvia & Richard Cruess Amphitheatre (ES1.1129)

McGILL CARDIOVASCULAR RESEARCH DAY

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Our sincere thanks to our judges for their expertise in scoring the abstracts submitted and to Ms. Line Dufresne for her technical assistance

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CME Accredited Event

This program meets the accreditation criteria as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada and has been accredited by the Office of Continuing Professional Development, Faculty of Medicine, McGill University for up to **4.75** Section 1 credits/hours.

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Acknowledgement of Institutional Sponsors

We acknowledge and greatly appreciate the support and involvement of our institutional sponsors as an integral part of the McGill Cardiovascular Research Day.

- McGill University Heath Centre – Research Institute
- Faculty of Medicine
- Department of Medicine

Schedule

Wednesday, May 29, 2019
Research Institute of the McGill University Health Centre
Drs. Sylvia & Richard Cruess Amphitheatre (ES1.1129)

7:30 – 8:20	Registration – *RI MUHC Atrium (ES1)*
8:15 – 8:25	Introduction Dr. Negareh Mousavi
8:25 – 8:30	Opening Remarks Dr. James Martin
8:30 – 9:50	Oral Presentations Session Chairs: Dr. Lawrence Rudski / Dr. Marco Spaziano
9:50 – 10:10	Break – RI MUHC Atrium (ES1)
10:10 – 11:10	Oral Presentations Session Chairs: Dr. Matthias Friedrich / Dr. Jonathan Afilalo
11:10 – 12:00	Poster Presentations – *RI MUHC Atrium (ES1)*
12:00 – 1:00	Keynote speaker ***"The implications of the proprotein convertases in the regulation of cardiovascular and metabolic functions"*** **Nabil G. Seidah, PhD** Director of Laboratory, Biochemical Neuroendocrinology, Institut de Recherches Cliniques de Montréal (IRCM) Professor, Biochemistry/Medicine, University of Montreal Adjunct Professor, Medicine, McGill University
1:00 – 2:00	Lunch – *RI MUHC Atrium (ES1)*
2:00 – 3:20	Oral Presentations Session Chairs: Dr. Ariane Marelli / Dr. Michael Goldfarb
3:20 – 4:30	Poster Presentations – *RI MUHC Atrium (ES1)*
4:30 – 5:00	Judges' Meeting Session Chairs' Table
4:30 – 5:30	Awards / Refreshments – *RI MUHC Atrium (ES1)* Closing remarks Dr. Negareh Mousavi / Dr. Jonathan Afilalo / Dr. Michael Goldfarb

Oral Presentations

8:30 – 8:50 ***ORAL #1 – Olga Berillo***
Genes of a Brown Norway chromosome 2 fragment introgressed into hypertensive Dahl salt-sensitive background exert pro-inflammatory effects when stimulated by a high-salt diet

8:50 – 9:10 ***ORAL #2 – Hao Yu Chen***
Identification of Novel Genetic Loci for Aortic Stenosis Through a Meta-Analysis of Genome-Wide Association Studies

9:10 – 9:30 ***ORAL #3 – Sunny Wei***
Approaches to Increase Statin Eligibility Among Individuals with Premature Acute Coronary Syndromes: An Analysis of the PRAXY Cohort

9:30 – 9:50 ***ORAL #4 – Malik Elharam***
Anticoagulant use and the risk of thromboembolism and bleeding in post-operative atrial fibrillation following non-cardiac surgery

9:50 – 10:10 Coffee Break

10:10 – 10:30 ***ORAL #5 – Rasha Al-Nadabi***
Triggered Cardiogenesis in Wingless 11 Treated Amniotic Mesenchymal Stromal Cells

10:30 – 10:50 ***ORAL #6 – Richard Zhang***
Prediction of Aortic Stenosis using Machine Learning Methods

10:50 – 11:10 ***ORAL #7 – Ahmad Mahmoud***
ROLE OF Vγ6+ γδ T CELLS IN ANGIOTENSIN II-INDUCED HYPERTENSION AND VASCULAR INJURY

Poster Presentations

11:10 – 12:00 Poster presentations

Keynote Speaker

Nabil G. Seidah, PhD, OQ, MRSC, MC

Director of Laboratory, Biochemical Neuroendocrinology, Institut de Recherches Cliniques de Montréal (IRCM)
Professor, Biochemistry/Medicine, University of Montreal
Adjunct Professor, Medicine, McGill University

Dr. Seidah obtained his BSc in 1969 from Cairo University in Egypt, and his PhD in 1973 from Georgetown University, USA. In 1974, he started studying the processing of precursor proteins at the Montreal Clinical Research Institute (IRCM), and in 1976 he co-discovered the β-endorphin and largely contributed to the biochemical characterization of the proopiomelanocortin (POMC, the β-endorphin precursor) and pro-Atrial Natriuretic factor. Since 1983, Dr Seidah is the director of Laboratory of Biochemical Neuroendocrinology.

Dr. Seidah discovered and cloned seven (PC1, PC2, Furin, PC4, PC5, PACE4, PC7, SKI-1 and PCSK9) of the nine known secretory serine proteases belonging to the proprotein convertases family. During this period, he also greatly contributed to demonstrating that proteolysis by the proprotein convertases is a widely used mechanism that also affects “non-neuropeptide” proteins such as growth factors, α-integrins, receptors, enzymes, membrane-bound transcription factors, and bacterial and viral proteins. In 2003, he identified PCSK9 and showed that point mutations in the PCSK9 gene cause dominant familial hypercholesterolemia, since PCSK9 gain-of-function mutations were linked to the ability of PCSK9 to enhance the degradation of cell surface receptors, such as the low-density lipoprotein receptor (LDLR). Dr Seidah has since worked on the elucidation of the functions and mechanisms of action of PCSK9 both in cells and in vivo, and is developing specific PCSK9 inhibitors.

Over the last 44 years, Dr. Seidah has attracted more than 146 graduate students, trainees and post-doctoral fellows. He is a member of numerous scientific associations including the Cancer Research Society and the American Heart Association. In 1991, he was elected fellow of the Royal Society of Canada. Dr Seidah is the recipient of several awards, including the 1995 Medical Research Council Scientist Award, he has been a member of the Order of Quebec since 1997 and of the Order of Canada since 1999. In 2001, he received the McLaughlin Medal of the Royal Society of Canada and the Parizeau Prize of the Association Canadienne-Française pour l'Avancement des Sciences (ACFAS). Since 2003 Dr Seidah has been endowed with a Tier-1 Canada chair on “Precursor Proteolysis”. In 2009 he received the Pfizer Distinguished Cardiovascular-Metabolic Research Jean-Davignon Award. In 2011, he was awarded the Wilder Penfield prize for the best scientist in Québec working in the biomedical field. In 2013, he was awarded the Queen Elizabeth II Diamond Jubilee Medal. In 2014, he received in Winnipeg the “Jacques Genest” Lecturer Award from the Canadian Society of Endocrinolgy and Metabolism. In 2016, he was selected as the recipient of the annual CIHR-ICRH Distinguished Lecturer Award in Cardiovascular Sciences in Canada. In 2018, he was selected for the prestigious Akira Endo Award for his seminal contributions to PCSK9 that led to a new powerful treatment for atherosclerosis, and was also awarded the major Lefoulon Delalande Award of the Institut de France for Research & Innovation in cardiovascular disease, as well as the 2018 McGill University Louis and Artur Lucian Award for research in circulatory diseases. On August 12, 2018 Dr Seidah was selected by La Presse as the personality of the week.

He has been invited as a speaker nationally and internationally to give more than 450 presentations, and over the years Dr Seidah gave more than 20 plenary lectures worldwide. In 1995, he organized the first Keystone conference on proprotein convertases. In 2006 he was the chairman of a prestigious Gordon Research Conference on "Proprotein Processing, Trafficking and Secretion" (Colby Sawyer College, NH, USA). Dr Seidah has been selected to present the prestigious “Jacques Benoît” lecture at the 7th International Congress of Neuroendocrinology held in Rouen France in July 2010. In 2013 he was invited to present the “Simon Pierre-Noël Memorial Lecture” at the Canadian Lipoprotein Conference in Mont-Tremblant, Québec, Canada.

Dr Seidah is internationally recognized as a world leader in convertases and their physiological roles. His numerous publications that tally more than 735 peer reviewed manuscripts have been widely recognized, and in fact he is cited as the most recognized protease expert in Canada and 6th worldwide. Indeed, Pubmed cites N.G. Seidah as the topmost in Canada and the 1st out of the worldwide 20 top scientists working on “Proprotein Convertases” since 1971. His H index = 93 (Web of Science), and his work has been cited more than 33,500 times.

Oral Presentations

2:00 – 2:20 ***ORAL #8 – Julia Rodighiero***
Restricted Median Survival Time of Older Adults Referred For But Not Undergoing Transcatheter Aortic Valve Replacement

2:20 – 2:40 ***ORAL #9 – Michelle Samuel***
Catheter ablation is associated with reduced all-cause mortality in a real-world cohort of patients with atrial fibrillation and heart failure

2:40 – 3:00 ***ORAL #10 – Ahmed Al-Turki***
Cardiac Resynchronization Therapy Reprogramming to Improve Electrical Synchrony in Patients with Existing Devices

3:00 – 3:20 ***ORAL #11 – Elizabeth Hillier***
Myocardial and Cerebral Oxygenation Deficits in Heart Failure – A Multi-Parametric Study

Poster Presentations

3:20 – 4:30 Poster presentations

4:30 – 5:00 Judges' meeting

Awards / Cocktails

4:30 – 5:30 Awards / Cocktails

Abstracts for Oral Presentations

8:30 – Olga Berillo

Genes of a Brown Norway chromosome 2 fragment introgressed into hypertensive Dahl salt-sensitive background exert pro-inflammatory effects when stimulated by a high-salt diet

Olga Berillo, Sofiane Ouerd, Ku-Geng Huo, Asia Rehman, Chantal Richer, Daniel Sinnett, Anne E. Kwitek, Pierre Paradis, Ernesto L. Schiffrin

Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada

Background: Chromosome 2 (Chr2) introgression from normotensive Brown Norway (BN) rats into hypertensive Dahl salt-sensitive (SS) background (consomic SB2) reduced blood pressure (BP) and vascular inflammation under normal-salt diet (NSD). We hypothesized that BN Chr2 contains anti-inflammatory genes that could reduce BP elevation and vascular inflammation in rats fed NSD and high-salt diet (HSD).

Method: Four- to 6-week old male SS and congenic rats containing the BN Chr2 distal portion (SB2a) and middle segment (SB2b) were fed NSD or HSD (4% NaCl) for 8 weeks. Systolic BP (SBP) by telemetry, reactive oxygen species (ROS) generation using dihydroethidium staining, and vascular cell adhesion molecule 1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1) expression and monocyte/macrophage (MoMφ) infiltration by immunofluorescence in aorta or perivascular fat (PVAT) were determined. RNA was extracted from aorta and used for small and total RNA sequencing and data were analyzed using a systems biology approach. Differentially expressed genes (DEGs) were identified with fold change >1.3 and fold discovery rate <0.05 and some of them were validated with RT-qPCR.

Results: SS SBP was 145±2 mm Hg under NSD and 168±1 mm Hg under HSD, which was lower in SB2a and SB2b SBP (125±3 and 127±6, P<0.05) under NSD but similar under HSD. Examination of ROS generation, VCAM-1 and MCP-1 expression and MoMφ infiltration revealed that SB2a present less and more inflammation under NSD and HSD, respectively, compared to SS. DEGs were identified in SB2a vs SS uniquely under NSD (15↑ and 8↓) and HSD (318↑ and 221↓) and under both diet (3↑ and 3↓), and in SB2b vs SS uniquely under NSD (43↑ and 65↓) and HSD (4↑ and 7 ↓) and under both diet (3↑ and 4 ↓). DEGs encoded within BN Chr2a were uniquely identified under NSD (1↑ and 1↓) and HSD (6↑ and 1↓), and in both diets (1↑ and 1↓). Gene enrichment analysis revealed that under NSD, 2 BN Chr2a DEGs are involved in regulation of BP, and under HSD, 7 BN Chr2a DEGs in cell proliferation, cell differentiation, signal transduction and the immune system. RT-qPCR validated DEGs encoded within BN Chr2a under NSD (2) and HSD (4).

Conclusions: DEGs encoded within BN Chr2a fragment are associated with anti- and pro-inflammatory effects under NSD and HSD, respectively.

Keywords: congenic rats, genetics, RNA sequencing, blood pressure, inflammation

8:50 – Hao Yu Chen

Identification of Novel Genetic Loci for Aortic Stenosis Through a Meta-Analysis of Genome-Wide Association Studies

Chen HY, Helgadottir A, Levinson RT, Shaffer C, Small AM, Damrauer SM, Martinsson A, Dina C, Cairns BJ, Hoekstra M, Burr HA, Manousaki D, Munter HM, Johansson B12, Naslund U, Ljungberg J12, Dufresne L, Ranatunga DK, Whitmer RA, Gudnason V, O'Donnell CJ, Rotter JI, Post W, Soderberg S, Richards JB,..., Lathrop M, Engert JC, Thanassoulis G

McGill University Health Centre, Montreal, Canada

Background: Aortic stenosis is the most prevalent clinical valve disorder in industrialized nations, affecting >12% of individuals older than 75. However, no medical therapy exists for the disease. Recent genome-wide association studies (GWAS) have identified few genetic loci but a meta-analysis of GWAS results for aortic stenosis may offer increased power to identify etiological loci and pathways, which may inform the development of novel medical therapies.

Methods: We performed inverse-variance weighted fixed-effects meta-analyses for each of 11,591,806 variants using GWAS results from 10 European-ancestry aortic stenosis cohorts totalling 652,134 participants (n=13,758 cases). For the variants which were genome-wide significant (p≤5e-8), we assessed whether consistent associations were observed in other ethnicities, as well as for aortic valve calcium, a subclinical precursor to aortic stenosis. We also performed gene-based analyses to identify additional loci associated with increased risk of aortic stenosis and gene-set analyses to identify pathways and co-regulated groups of genes that may be differentially expressed in patients. The false discovery rate was applied where appropriate to account for multiple testing.

Results: We identified nine variants which demonstrated novel associations with aortic stenosis, including in two loci involved in inflammatory response. We observed directionally-concordant associations for several of these variants with aortic stenosis in non-European participants or with aortic valve calcium. We also confirmed the association of all variants previously identified for aortic stenosis (n=8). Gene-based analyses further identified loci involved in lipid metabolism and gene-set analyses indicated that transcription and post-transcriptional regulation of certain gene groups is associated with disease status.

Conclusions: We have identified several novel loci that are associated with aortic stenosis risk, strengthening evidence that aortic stenosis is a polygenic disease characterized by disordered inflammatory responses and lipid metabolism. Additional work is required to assess the potential of these loci for therapeutic targeting and risk prediction.

Keywords: Aortic stenosis, Genome-wide association study, Meta-analysis, Lipid metabolism, Inflammation

9:10 – Sunny Wei

Approaches to Increase Statin Eligibility Among Individuals with Premature Acute Coronary Syndromes: An Analysis of the PRAXY Cohort

Wei S, Pilote L, Dufresne L, Engert JC, Sniderman AD, Thanassoulis G

McGill University Health Centre, Montreal, Canada

Background: Premature acute coronary syndromes (ACS) still account for approximately a third to half of all ACS cases. Evidence from clinical trial data demonstrates that the use of statins for primary prevention decreases the risk of cardiovascular events, and this effect appears larger in young low risk individuals. However, current dyslipidemia guidelines focus on 10-year risk estimation and therefore capture only a limited group of young adults at risk for premature ACS. We sought to estimate the number of individuals who would be eligible based on alternative strategies for statin eligibility.

Methods: 508 potentially statin eligible participants from the GENESIS-PRAXY cohort of adults <55 years old who were hospitalized for ACS, were included. We compared statin eligibility through 4 separate approaches: the current 10-year risk-based approach (>=7.5% via Pooled Cohort Equation), a short-term benefit-based approach (absolute risk reduction over 10 years [ARR10] >= 2.3%, equivalent to number needed to treat of 44 in current guidelines), a long-term benefit-based approach (ARR30 >= 15%, consistent with minimum expected 30-year benefit in individuals with low-density lipoprotein cholesterol [LDL-c] levels compatible with genetic dyslipidemias) and the use of genetic risk scores (90th percentile cut-off derived from Multi-Ethnic Study of Atherosclerosis).

Results: The risk-based approach captured 31.7% (95% CI: 27.7-36.0%) of the cohort, whereas the short and long-term benefit-based approaches captured 47.4% (95% CI: 43.0-51.9%) and 44.9% (95% CI: 40.5-49.3%) respectively. This represents an additional ~13-15% of ACS cases who were not statin eligible under current guidelines, but who had the same or greater expected benefit from statins. Incorporation of genetic risk scores captured an additional 11.0% (95% CI: 7.8-15.2%) of the cohort, a fraction independent from participants identified through risk scores or benefit-based approaches. Specifically, the risk-based approach selected for older participants, with a history of smoking, whereas the benefit-based approaches selected for younger participants with higher LDL-c levels. On the other hand, participants identified through genetic risk scores revealed no obvious discernable features with regard to traditional cardiovascular risk factors. Approximately a third of the cohort remained uncaptured by any approach.

Conclusion: Both the benefit-based approaches and genetic risk scores identify additional premature ACS cases who would be potentially statin eligible, independent of those captured through current risk calculators. Given that statin use is effective in young adults, the incorporation of these approaches into current guidelines could better identify young adults who would derive significant benefit from statin use.

Keywords: Premature Acute Coronary Syndrome, Statin, Primary Prevention, Guidelines

9:30 – Malik Elharam

Anticoagulant use and the risk of thromboembolism and bleeding in post-operative atrial fibrillation following non-cardiac surgery

Malik Elharram, Michelle Samuel, Michael Quon, Hassan Behlouli, Amal Bessissow, Louise Pilote

McGill University Health Centre, Montreal, Canada

Background: While post-operative atrial fibrillation is associated with a high incidence of long-term thromboembolic events, a lack of data exists to support an anticoagulation strategy in non-cardiac surgical patients. We aim to determine if anticoagulation use is associated with a reduction in thromboembolic events or an increase in bleeding in patients with new atrial fibrillation after non-cardiac surgery.

Methods: A retrospective cohort was used to identify patients with a new diagnosis of atrial fibrillation after non-cardiac surgery. Initiation of anticoagulation was defined as prescription of an oral anticoagulant within 30 days of hospital discharge. Time to first hospital admission or emergency department visit for a thromboembolic event (including ischemic stroke and transient ischemic attack) or major bleeding event were compared using Cox regression models adjusted for potential confounders from the CHA2DS2VASc and HASBLED scores.

Results: We studied 22,007 patients with a new diagnosis of atrial fibrillation after non-cardiac surgery (mean age: 75 years). The entire cohort was largely at high thromboembolic risk (90% with CHADS2VAsc≥2) and underwent mainly thoracic (30%) and abdominal (24%) surgeries. Overall, 6475 (30%) patients were initiated on anticoagulation. During a mean follow up of 5 years, 1202 (6%) patients had a thromboembolic event, and 4188 (19%) had a major bleeding event. Among patients at high risk (CHADS2VAsc ≥2), the incidence of a thromboembolic event was similar in those anticoagulated (1.3 per 100 person-years, 95% CI 1.2-1.4) compared to those without (1.2 per 100 person-years, 95% CI 1.1-1.4). We did not find an association between anticoagulation use and a lower incidence of thromboembolic events (HR: 0.90, 95% CI 0.8-1.02). However, anticoagulation use was associated with a slightly higher risk of bleeding (HR: 1.1, 95% CI 1.0-1.15).

Conclusion: In patients with new atrial fibrillation after non-cardiac surgery, we did not find an association between anticoagulation use and a reduction in thromboembolic events. Our results suggest that anticoagulation in this population could be associated with a slightly higher risk of bleeding.

Keywords: Atrial Fibrillation, Anticoagulation, Cardiovascular Outcomes

10:10: Rasha Al-Nadabi

Triggered Cardiogenesis in Wingless 11 Treated Amniotic Mesenchymal Stromal Cells

Al-Nadabi R, Makhoul G, Khan K, Yu B, Schwertani A, Cecere R

McGill University Health Centre, Montreal, Canada

Introduction: In vitro cardiomyogenic transdifferentiation remains evasive and the injured cardiac myocytes are constantly destined to undergo apoptosis. To circumvent these limitations, stem cell plasticity presents a reliable source that could replenish the dead cardiac myocytes. Accordingly, intense research efforts are being focused on finding specific molecular triggers that could promote the acquisition of a cardiomyocytic phenotype to stem cells. In this context, it was observed that Wingless 11 (Wnt-11), a ligand of the Wingless pathway, is expressed early in cardiac morphogenesis, giving rise to embryonic heart fields. Herein, we have examined the cardiogenic potential of Wnt-11 on amnion-derived mesenchymal stromal cells.

Methods: Amniotic mesenchymal stromal cells (AMSCs) were initially scanned for a battery of cardiac-specific genes. To determine an optimized dose-dependent effect, cardiac gene analyses were conducted on AMSCs treated with increasing concentrations of Wnt-11 at different time intervals. The metabolic activity of Wnt-11 treated AMSCs was then investigated using an Alamar Blue assay. Subsequently, immunofluorescence staining was conducted on cardiac-specific proteins. Intra-cellular calcium influx was then measured in AMSCs and observed under live imaging.

Results: Gene expression analyses revealed that the AMSCs constitutively express ample cardiac-specific genes. In Wnt-11 treated AMSCs, gene expression levels differed according to Wnt-11concentrations, with 100 ng/ml for 3 days presenting a significant fold increase in a multitude of cardiac-specific genes. This optimal dose of Wnt-5a did not alter the AMSCs' viability and proliferation rates. Moreover, a significant increase in protein expression of GATA4 and sarcoplasmic reticulum calcium-ATPase2a (SERCA2a) was detected in the Wnt-11 treated AMSCs compared to control cells. Interestingly, under live imaging, the intracellular calcium signaling was significantly enhanced in Wnt-11 treated AMSCs.

Conclusions: The constitutive expression of ample cardiac-specific genes underscores the advantages of AMSCs for cardiac lineage differentiation. Treatment with an optimized dosage of Wnt-11 enabled further cardiogenic commitment and upregulated cardiac-specific markers at the genetic and proteomic levels. This upregulation was complemented with an increased and regulated intracellular calcium influx. Hence, a temporal treatment of AMSCs with Wnt-11 could be considered a promising strategy to replenish the cardiac myocytes lost in heart disease.

Keywords: Stem cell, Wingless, Cardiogenesis

10:30 – *Richard Zhang*

Prediction of Aortic Stenosis using Machine Learning Methods

Zhang R, Chen HY, Nagai Y, Dufresne L, Ambikkumar A, Thanassoulis G, Engert J

McGill University Health Centre, Montreal, Canada

Background: Aortic stenosis (AS) is a serious cardiovascular disease that predominantly affects older individuals. It is characterized by reduced blood flow due to a constriction of the aortic valve. Genome-wide association studies (GWAS) have uncovered genetic variants with significant associations with AS. Machine learning methods can be used to investigate the total predictive power of these genetic variants and to potentially incorporate complex gene-gene or gene-environment interactions.

Methods: Clinical and genetic data were obtained from a European-ancestry case-control dataset (n=55,192) from the Genetic Epidemiology Research on Aging cohort. We investigated the predictive power of logistic regression (LR) with least absolute shrinkage and selection operator, linear support vector machines (SVM), and neural networks (NN) for AS using either clinical data only, genetic data only, or both clinical and genetic data combined. Twenty percent of the samples (n=11,039) were reserved as a final test set; the remaining samples (n=44,153) were used for fitting and hyperparameter tuning. Model performance was evaluated based on various metrics including F1 scores and receiver operating characteristic curves.

Results: In the validation stage the best LR and NN models achieved equally good results; SVM models had slightly worse performance. On the test set however, NN performance was worse than both of the linear models. SVM and LR both achieved F1 scores of 0.3 and AUCs of 0.81 when trained on clinical data. With genetic data, SVM and LR reached F1 scores of 0.61 and AUCs of 0.94. On the combined data, LR achieved a F1 score of 0.72 and AUC value of 0.97 while SVM had an F1 score of 0.69 and an AUC value of 0.97.

Conclusions: Linear models show great performance with regards to differentiating AS cases and controls when using both clinical and genetic data as indicated by the high AUC values. Lower F1 scores are driven by a significant chance for predicted cases to be false positives. A lack of significant improvement of NN models may be due to a lack of easily captured complex interactions such as gene-gene or gene-environment interactions. The genetic variables are more predictive for AS status than the clinical variables, but clinical variables still contribute when added to the genetic information. These results provide evidence that clinical and genetic data capture different aspects of AS disease prediction. An analysis of model weights will reveal important factors for AS prediction and may uncover new associations or reaffirm existing ones.

Keywords: Aortic Stenosis, Machine Learning, GWAS

10:50 – Ahmad Mahmoud

ROLE OF Vγ6+ γδ T CELLS IN ANGIOTENSIN II-INDUCED HYPERTENSION AND VASCULAR INJURY

Mahmoud A, Caillon A, Paradis P, Schiffrin E

Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada

Introduction: Both innate and adaptive immune cells (such T lymphocytes) have been shown to play a role in hypertension and vascular injury. Recently, we have demonstrated that a small subpopulation of T cells considered "innate-like", expressing the T-cell receptor (TCR) γδ rather than the much more frequent αβ TCR, plays a key role in hypertension and vascular injury. The number and activation of γδ T cells were increased after 7 days of angiotensin (Ang) II infusion, and absence of γδ T cells prevented the development of hypertension, endothelial dysfunction of resistance arteries, and activation of CD4+ and CD8+ T cells in mice infused with Ang II for 14 days. γδ T cells can be subdivided according to the TCR variant (V) subtype that is generally specific for a tissue. A subpopulation of γδ T cells in the lungs and skin that are Vγ6+ and produce interleukin (IL)-17A was shown to respond promptly to pneumococcal infection and skin inflammation. However, γδ T cell Vγ subtypes involved in hypertension are still unknown. We hypothesized that γδ T cells involved in hypertension are Vγ6+.

Methods: Eleven- to 13-week old C57BL/6J male mice were infused or not with Ang II (490 ng /kg /min, sc) for 14 days (n = 5-14), and γδ T cell Vγ subtypes were profiled by flow cytometry in the spleen, mesenteric lymph nodes (MLNs), thoracic aortic (TA), perivascular adipose tissue (PVAT) and mesenteric artery (MA) PVAT.

Results: In spleen and MLNs the most abundant γδ T cell Vγ subtypes were Vγ1,2+ and Vγ4+ followed by Vγ6+, Vγ5+ and Vγ7+. In TA PVAT, the most abundant γδ T cell Vγ subtype was Vγ6+ followed by Vγ4+, Vγ1,2+, Vγ5+ and Vγ7+. In MA PVAT, the most abundant γδ T cell Vγ subtype was Vγ6+ followed by Vγ4+, Vγ7+, Vγ5+ and Vγ1,2+. Ang II infusion increased the frequency of Vγ6+ γδ T cells in the spleen (% of CD3+ T cells: 0.77±0.09 vs. 0.5±0.02, P<0.01) and TA PVAT 5.9±0.8 vs. 3.6±0.4, P<0.01), whereas it only tended to increase in MA PVAT 14.5±1.7 vs. 10.2± 1.9, P=0.07). The Vγ6+ γδ T cell frequency in MLNs was unaffected by Ang II infusion.

Conclusion: Different distribution of γδ T cell Vγ subtypes was observed in lymphoid organs compared to PVATs. Vγ6+ γδ T cells may play a role in hypertension. Targeting Vγ6+ γδ T cells could be a therapeutic approach to reduce inflammation in hypertension.

Keywords: VÎ³6+, Î³Î´ T cells, PVAT, Hypertension, Angiotensin II

2:00 – Julia Rodighiero

Restricted Median Survival Time of Older Adults Referred For But Not Undergoing Transcatheter Aortic Valve Replacement

Julia Rodighiero, Nicolo Piazza, Giuseppe Martucci, Marco Spaziano, Kevin Lachapelle, Marie-Claude Ouimet, Jonathan Afilalo

Jewish General Hospital, Montreal, Canada

Introduction: A subpopulation of older patients with severe symptomatic aortic stenosis are referred for transcatheter aortic valve replacement (TAVR) but do not undergo any procedure. We sought to categorize the clinical and geriatric profiles of patients not undergoing TAVR, and determine each profile's projected survival using restricted median survival time (RMST).

Methods: Older adults assessed between 2014-2018 at the McGill University Health Center TAVR clinic were prospectively enrolled. In addition to patients who underwent TAVR (Group A), those who did not undergo a valve replacement procedure within one year of their clinic evaluation were categorized according to the following reasons: patient (Group B) or physician (Group C) decision not to proceed, waiting for the procedure or for a decision to be made (Group D), undergoing balloon valvuloplasty as a potential intermediate to TAVR (Group E). The RMST and Cox proportional hazard ratio for mortality were computed over 1 year. Patient-level predictors for not undergoing TAVR were examined using multivariable logistic regression.

Results: The cohort consisted of 377 patients with a mean age of 82.3 years, of which 233 underwent TAVR and 144 did not. Relative to group A (N=233), the difference in the adjusted RMST was -29 days (95% CI -67, 8) in group B (N=24), -36 days (95% CI -63, -10) in group C (N=68), -141 days (95% CI -203, -78) in group D (N=29), and 5 days (95% CI -29, 38) in group E (N=23). This corresponded to an adjusted hazard ratio for mortality of 3.64 in group B (95% CI 1.50, 8.84), 3.75 in group C (95% CI 1.93, 7.23), 14.00 in group D (95% CI 6.70, 29.25), and 1.33 in group E (95% CI 0.45, 3.93). Kaplan-Meier survival curves were superimposed for TAVR and valvuloplasty patients until approximately 8 months, after which, valvuloplasty patients accrued more fatalities. Patient-level predictors for not undergoing TAVR were: age ≥90 years, high Essential Frailty Toolset score (poor chair-rise performance and cognitive impairment), disability for basic activities of daily living, severe lung disease, severe kidney disease, and reduced left ventricular ejection fraction ≤35%.

Conclusion: Older patients who are referred for TAVR but do not undergo a procedure have reduced survival time, especially when waiting for the TAVR procedure or decision. Those undergoing a valvuloplasty appear to be protected for approximately 8 months. Efforts should be made to minimize TAVR wait times or consider balloon valvuloplasty when a TAVR decision is deferred.

Keywords: Restricted Mean Survival Time, Older Adults, TAVI Deferral, Severe Aortic Stenosis

2:20 – Michelle Samuel

Catheter ablation is associated with reduced all-cause mortality in a real-world cohort of patients with atrial fibrillation and heart failure

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Abstract has been withdrawn at the presenter's request.

2:40 – Ahmed Al-Turki

Cardiac Resynchronization Therapy Reprogramming to Improve Electrical Synchrony in Patients with Existing Devices

AlTurki A, Yuri P, Garcia D, Montemezzo M, Al-Dosari A, Vidal A, Toscani B, Diaz S, Bernier M, Hadjis T, Joza J, Essebag V.

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Background: Optimal programming of cardiac resynchronization therapy (CRT) has not yet been fully elucidated. A novel algorithm (SyncAV) has been developed to improve electrical synchrony by fusion of the triple wavefronts: intrinsic, right ventricular (RV)-paced, and left ventricular (LV)-paced. Whether electrical synchrony can be improved in patients with a chronically implanted CRT has not been proven. Therefore, we aimed to assess the difference in QRSd in patients with a previously implanted CRT who subsequently receive SyncAV pacing compared to existing chronic CRT pacing as well as another proprietary device-based timing cycle optimization algorithm (QuickOptTM).

Methods: Consecutive patients at a single tertiary care center with a previously implanted CRT device with SyncAV algorithm (programmable negative AV hysteresis) were evaluated. QRS duration (QRSd) was measured during 1) intrinsic conduction, 2) existing CRT pacing as chronically programmed by treating physician, 3) using the device-based QuickOpt™ algorithm for optimization of AV and VV delays, and 4) ECG-based optimized SyncAV programming. The paced QRSd was assessed and compared to intrinsic conduction and between the different modes of programming.

Results: Of 64 consecutive, potentially eligible patients who underwent assessment, 34 patients who were able to undergo SyncAV programming were included. Mean intrinsic conduction QRSd was 163±24 ms. In comparison, the mean QRSd was 152±25 ms (-11.1±19.0) during existing CRT pacing, 160±25 ms (-4.1±25.2) using the QuickOpt™ algorithm and 138±23 (-24.9±17.2) using ECG-based optimized SyncAV programming. Using SyncAV optimization resulted in significant reduction in QRSd compared to existing CRT pacing (-13.8±12.4, P=0.02) and the QuickOpt™ algorithm (-21.1±17.8, P<0.001). Of the 32% of patients who did not have QRS narrowing with existing CRT, 72% experienced QRS narrowing with SyncAV. After multivariate analysis, only QRSd with existing CRT pacing predicted a reduction in QRSd with SyncAV.

Conclusion: ECG-based atrio-ventricular delay optimization using SyncAV significantly improved electrical synchrony in patients with a previously implanted CRT. Further studies are needed to assess the impact on long-term outcomes.

Keywords: cardiac resynchronization therapy, pacemaker, heart failure

3:00 – Elizabeth Hillier

Myocardial and Cerebral Oxygenation Deficits in Heart Failure - A Multi-Parametric Study

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Introduction: Cognitive decline is a known co-morbidity of Heart Failure. Many different pathophysiological mechanisms have been suggested as etiologies underlying the development of cognitive impairment such as cerebral hypoperfusion as a result of reduced cardiac output, decreased cerebrovascular reactivity, microvascular dysfunction, arterial hypertension, and increased chronic proinflammatory response. Combining breathing manoeuvres developed to identify myocardial and cerebral oxygenation reserve deficits with blood oxygen level dependent (BOLD) properties of Oxygenation-Sensitive MRI (OS-MRI), this study applies OS-MRI to assess the tissue oxygenation response to breathing maneuvers in both the cerebrum and the myocardium.

Methods: Twelve heart failure patients (mean age 64±9 years; 36% female) and fourteen age-matched healthy volunteers (mean age 56±5 years; 64% female) underwent a CMR on a clinical 3T scanner (Skyra, Siemens, Erlangen, Germany). CMR functional parameters were obtained from standard SSFP long-axis cine images. OS CMR images were obtained in a basal and mid-ventricular short-axis slice. The global Myocardial Oxygenation Reserve (MORE) was obtained from oxygenation sensitive SSFP short-axis cine images acquired at resting baseline and continuously during a voluntary maximal breath-hold following a 60s period of hyperventilation. The cerebral BOLD images were obtained in the axial plane covering the full cerebrum. The global Cerebral Oxygenation Reserve (CORE) was obtained from subtracting images delineating the global signal intensity differences obtained on BOLD images in the grey matter of the brain.

Results: Heart failure patients (LVEF=40.98+/-14.18%) had a significantly lower left ventricular ejection fraction (LVEF) when compared to healthy controls (LVEF=69.46+/-6.79%) (p<0001). The percent-change in signal intensity in brain grey matter (CORE) and the global myocardium (MORE) after breathing maneuvers were significantly reduced in patients when compared to healthy controls (mean CORE 0.29+/-0.63 vs. 1.083+/-0.5047, p=0.0021, mean MORE 0.2497+/-3.495 vs. 4.451+/-4.15, p=0.0131) (Fig 1). There is a significant correlation between CORE and LVEF in heart failure patients with a Pearson correlation coefficient r=0.642, and a coefficient of determination r^2=0.4123, p=-0.032 (Fig 2).

Conclusion: The significant reduction of both cerebral and myocardial oxygenation reserves in heart failure patients when compared to healthy control subjects indicated that microvascular dysfunction of both the cerebrum and myocardium are present in heart failure patients. The presence of a significant correlation between LVEF and CORE suggests that microvascular dysfunction in the brain may be a result of chronic hypoperfusion.

Keywords: Heart Failure, Cognitive Impairment, CMR, Heart Brain Axis

Abstracts for Poster Presentations (listed alphabetically)

Effects of preeclampsia on cardiac and sympathetic baroreflex sensitivity in the post-partum period

Adler TE, Leone C, Paidas MJ, Stachenfeld NS, Usselman CW

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Background: Preeclampsia, a pregnancy complication characterized by new-onset hypertension and proteinuria, is a leading cause of maternal mortality worldwide. Moreover, life-long rates of cardiovascular morbidity and mortality remain high in women who have had preeclamptic pregnancies. Autonomic control of blood pressure in this population of women remains poorly understood. The purpose of this study was to evaluate the effects of a recent preeclamptic pregnancy on baroreflex function, the primary autonomic reflex involved in blood pressure regulation. We hypothesized that otherwise healthy women with a recent history of preeclampsia would exhibit attenuated baroreflex sensitivity, via both the cardiovagal and sympathetic arms of the reflex.

Methods: We compared spontaneous baroreflex function in women with recent healthy (CTRL; n=7) and preeclamptic (PE; n=6) pregnancies. All were free from overt cardiovascular or endocrinological disease and none were breastfeeding. By design, age, BMI, and months post-partum were similar between groups (CTRL vs PE: 28±2 vs 31±6 yrs, P=0.4; 27±3 vs 29±5 kg/m2, P=0.5; 15±5 vs 17±4 months, P=0.3). Muscle sympathetic nerve activity (microneurography), heart rate (ECG), and beat-to-beat blood pressure (Finometer) were assessed during 10 minutes of quiet rest.

Results: Resting blood pressures were similar between groups (systolic: 120±11 vs 111±12 mmHg; diastolic: 75±10 vs 70±8 mmHg). Cardiovagal baroreflex gain (sequence method) did not differ between CTRL and PE groups (21.6±12.1 vs 16.2±4.8 ms/mmHg; P=0.2). Relative to CTRL, PE had higher sympathetic burst incidence (15.7±5.2 vs 30.0±9.8 bursts/100hb; P=0.01). Sympathetic baroreflex function, as assessed by the linear relationship between sympathetic burst incidence and diastolic blood pressure, did not differ between CTRL and PE groups (-3.0±1.9 vs -3.8±1.5 bursts/100hb/mmHg; P=0.2).

Conclusion: Despite our observation of elevated muscle sympathetic nerve activity in women with a recent preeclamptic pregnancy, we found no evidence for baroreflex dysfunction during quiet rest. Future research may investigate autonomic responsiveness to sympatho-excitatory and -inhibitory stimuli in women with a recent history of pre-eclampsia. Understanding the function of autonomic reflexes and reactivity in this population may yield important mechanistic insights into the elevated cardiovascular risk experienced by women with a history of pre-eclampsia.

Keywords: preeclampsia, baroflex function, sympathetic nerve activity, blood pressure

Prediction of Familial Hypercholesterolemia in Patients at High Atherosclerotic Cardiovascular Disease Risk Using a Novel Computer Algorithm+

Alothman L, Zawadka M, Aljenedil S, Kajil M, Bewick D, Gaudet D, Hegele R.A., Lonn E, Ngui D, Ruel I, Singh N, Genest J, Gupta M, for the REACT investigators.

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Background: The prevalence of heterozygous familial hypercholesterolemia (FH) is 1/250 in the general population and ~1/125 in atherosclerotic cardiovascular disease (ASCVD) patients, yet only a minority are diagnosed. The diagnostic criteria for FH rely on a point system using LDL-C, family history, cutaneous manifestations and molecular diagnosis.

Objective: The aim of the present study was to determine the prevalence of FH in the REACT (Relating Evidence to Achieve Cholesterol Targets) registry. Methods: Patients were enrolled as either ASCVD (n=86) or FH (n=109) and an LDL-C level > 3.0 mmol/L despite maximally tolerated statin therapy. FH was diagnosed clinically using a validated computer algorithm integrating an imputation for baseline (untreated) LDL-C levels.

Results: There were 109 men and 86 women, mean age was 63±12 years. Diabetes (29.7%), hypertension (62.1%), smoking (37.9%) and family history of premature ASCVD (59.5%) were common. On-treatment LDL-C was 4.26±0.94 mmol/L. Based on the dose and type of statin ± ezetimibe, imputed baseline LDL-C was 7.04±2.90 mmol/L. A diagnosis of probable/definite FH was found in 54.7%, 49.5% and 61.5% of patients according to the Simon-Broome, Dutch Lipid Clinic Network criteria and the new Canadian FH definition, respectively. Interestingly, 40% of patients in the ASCVD inclusion subgroup had probable/definite FH.

Conclusion: Our study reveals that a substantial proportion of ASCVD patients whose LDL-C levels remain above target have heterozygous FH. Appropriate diagnosis of FH in these patients is important, as it should result in aggressive therapy and screening of first-degree relatives. Simplified tools for clinical FH diagnosis should enable clinicians to more easily identify FH patients in practice.

Keywords: familial hypercholesterolemia, ASCVD, imputed LDL

Sharing Experiences with Agile Software Development Methodology in the READYorNotTMe-Health Intervention for Brain-Based Disabilities

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Background: Lifespan conditions are increasing in prevalence as children survive to adulthood with chronic diseases such as brain-based disabilities (BBD). Transition from pediatric to adult care is a resource-intense and complex process that needs to engage health systems, patients, families, and intersectoral pediatric and adult care providers. Despite guideline recommendations that transition of care should be anchored to structured processes, few programs exist. There is thus a growing need for health interventions that bridge care between pediatric and adult providers by providing a Health Information Technology (HIT) solution.

Method: A multidisciplinary collaboration —combining thought leadership in clinical psychology, translational medicine, CHD and BBD, as well as patient and families' insights— was initiated to design, develop, and clinically validate the READYorNotTM e-Health intervention to educate and empower young adolescents as they undergo transition from pediatric to adult care.
In other to ensure that the e-health intervention can respond to all the stakeholders needs and particularly the adolescent users; there is a need to incorporate them on the HIT development process which includes the creation and validation of the HIT components such as the interface design, the content of the mobile and desktop applications and their features. Incorporating the patients, families and researchers' feedback while developing the HIT required to incorporate Agile software development methods which offer developers the necessary flexibility to adapt to changing user requirements and seem to facilitate user acceptance and project success.
The READYorNotTM is currently undergoing final usability testing (UAT) to ensure that the MyREADY TransitionTM App effectively meets end-user requirements, conforms quality standards, exposes technology deficiencies and unmet patient needs with the aim to maximize user experience and adherence.
The READYorNotTM intervention gaming approach in the form of a Journey in the City with a mentor that will help the user to navigate on the buildings, will sequentially introduce the 19 educational sections with videos and its skill-based-achievement challenges along the six weeks training curricula.

Conclusions: The READYorNotTM intervention is expected to improve quality of care and patient and family experiences during transition with a potential for reduction in cost that is expected to be translatable across pediatric and adult health care systems. Our findings are also expected to inform guidelines and policy recommendations for a growing number of patients with childhood conditions requiring life-long care; integrate family members and care givers or incorporate a community platform for all parties' participation in the future.

Keywords: transition of care, brain-based disabilities, e-health intervention, technology-development agile, patient centered design

Withdrawal of Beta- Blockers and ACE Inhibitors After Left Ventricular Systolic Function Recovery in Patient with Dilated Cardiomyopathy Randomized Control Study

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Introduction: Recovery of left ventricle (LV) systolic function with normalization of ejection fraction (LVEF) occurs in 10 - 27% of patients with 80% maintaining recovery. However, the need for medical therapy after recovery is often questioned. Previous randomized studies of treatment withdrawal were small, not selected for non-ischemic dilated cardiomyopathy (DCM) and had a reference of improved or recovered LVEF to > 40% or > 10% change from LVEF at time of diagnosis. Hypothesis: In patients with DCM with recovery of the LV systolic function to an EF (>50%), medical therapy withdrawal is possible without rebound LV systolic dysfunction.

Method: This was a pilot randomized control open-label trial with 2:1 randomization for withdrawal of b-blockers and ACE inhibitors in patients with recovered LV systolic function. Patients' medication discontinuation occurred in 2 phases with a six-month interval and patients were followed for one year. In phase 1, the b-blockers were withdrawn. In phase II, the ACE inhibitors were withdrawn. The primary endpoint was LVEF reduction (< 40%).

Results: There were 22 patients (10 females) enrolled. The mean age was 60 ± 12y. The mean LVEF at enrollment was 58 ± 5% with no significant difference in the mean LVEF in both groups. Sixteen patients were assigned to the withdrawal group and 6 assigned to the control group. The primary endpoint occurred in 44% of the withdrawal group compared to none of the control. Event free survival at 6 month and 1 year were 87.5% and 73% respectively, p-value 0.087. The mean LVEF at 1 year for the treatment withdrawal group was 46.8 ± 12% and control 55 ± 6%. The mean LVEF reduction was 10.6 ± 11%. The difference in the mean LVEF between the groups at 1 year was 8% with 95% CI (-3.3,20) at p-value 0.1. The difference in the mean LVEF at enrollment and at 1 year follow up for the medication withdrawal group was 10.6 ± 11% and 95% CI (4.6,16.49) with p-value 0.0017.

Conclusion: In DCM patients with recovery of LV systolic function, worsening of LVEF occurred after withdrawal of b-blockers and ACE inhibitors.

Keywords: cardiomyopathy, heart failure, medical therapy

The Lifelong Burden of Homozygous Familial Hypercholesterolemia

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Homozygous familial hypercholesterolemia (HoFH) is caused by mutations in the low-density lipoprotein receptor (LDLR) gene. It is diagnosed in children or youth presenting with extensive tendinous and cutaneous xanthomas and extreme elevation of LDL-C (> 13 mmol/L). Untreated, premature coronary artery disease develops in the teenage years or earlier and survival above 30 years of age is rare. Here we describe the clinical course of a patient with HoFH treated according to the standards of care and experimental approaches. Despite aggressive therapies, atherosclerosis in all vascular beds progressed, leading to the patient's demise at age 59.

Keywords: homozygous familial hypercholesterolemia, low density lipoprotein receptor, atherosclerosis, case report

From Silos to Integration: Comparing a Modality-Centered to a Patient-Centered Instructional Format for Multimodality Imaging

Sarah Blissett, Matt Sibbald, Christos Galatas, Annabel Chen-Tournoux, Pantelis Diamantouros, Jonathan Afilalo, Lawrence Rudski, Regina Husa, Igal A. Sebag

Jewish General Hospital, Montreal, Canada

Background: A key component in instruction of multimodality imaging (MMI) is the development of integrative skills that facilitate complementary use of modalities and rationalization of discrepant results. The current modality-centered format of instruction, where training programs focus on each modality in series, may be inadequate for the development of integrative skills. Incorporating MMI within a case in a patient-centered format could facilitate development of integrative skills. We compared integrative skills, general knowledge and transfer of knowledge between a modality-centered format and a patient-centered format for MMI instruction.

Material and Methods: In this multicenter study, Cardiology fellows were randomized to instruction with either the modality-centered or patient-centered format. Participants read the instructional materials independently. Both instructional formats contained information on 3 cardiac lesions (aortic regurgitation, hypertrophic cardiomyopathy and atrial septal defect) and 3 imaging modalities (echocardiography, cardiac magnetic resonance (CMR) and cardiac catheterization). The modality-centered format organized information by imaging modality. In the patient-centered format, the same information was incorporated into 3 cases. A written test addressing integrative skill, general knowledge and transfer of knowledge was completed independently. Scores were compared using t-tests.

Results: Thirty-four fellows from 4 institutions participated (modality-centered format n=18, patient-centered format n=16). The groups were similar on the basis of training level (4 vs 4 PGY 6 participants) and anticipated imaging-based specialization (7 vs 5 participants). The groups had similar exposure to echocardiography (3.1 vs 3.2 months), CMR (0.36 vs 0.23 months) and cardiac catheterization (1.8 vs 1.7 months). Integrative skill scores were significantly higher with the patient-centered format (46 22 vs 66 19%, p=0.011). There was no difference in general knowledge (75 14 vs 67 16%, p= 0.23) or transfer of knowledge (30 14 vs 22 16%, p=0.16).

Conclusion: The patient-centered format was associated with higher scores on integrative skill, encouraging incorporation of integrated, patient-centered formats into instruction of cardiac imaging in the Cardiology training curriculum.

Keywords: multimodality imaging, medical education, echocardiography, MRI, hemodynamic catheterization

The epidemiology of aortic stenosis in Quebec - A view from 70,000 feet with TAVR population and policy implications

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Background: Aortic stenosis (AS) is the most frequent valvular condition. Trans-catheter aortic valve replacement (TAVR) is a new, less invasive technology with at least comparable outcomes compared to surgical aortic valve replacement (SAVR). Examining AS epidemiology is important to discover under-treated populations and to assist in future planning for TAVR technology.

Methods: Population based study of all AS diagnoses and interventions occurring in the Province of Quebec from 2002 – 2010 using provincial administrative databases. AS events were directly standardized to the 2006 Quebec population.

Results: During the 9-year study period, there were 35,177 new AS diagnoses and 11,182 SAVR interventions. There was an association between an increasing age and an increasing incidence of AS diagnosis for both men and women, but higher diagnostic rates were observed for men compared to women in all age categories ($p < 0.001$). Similarly, there were higher intervention rates in men than women in both younger (rate ratio (RR) = 2.6, $p < 0.001$) and older age categories (RR = 1.8, $p < 0.001$). The proportion of interventions to diagnoses was less for patients ≥ 80 for both women (RR = 0.36, $p < 0.001$) and men (RR = 0.45, $p < 0.001$) compared to those under age 80. Overall, diagnostic and intervention rates increased over the study period, again disproportionally more for men than women.

Conclusions: This study suggests that particularly women and the elderly face an important diagnostic and treatment gap for AS. Acknowledging these gaps in medical care will be important in planning and allocating future resources for newer AS interventions.

Keywords: aortic stenosis, epidemiology, trans-catheter aortic valve replacement

Identifying the Genetic Determinants of Spontaneous Coronary Artery Dissection with Whole Exome Sequencing

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Background: Spontaneous Coronary Artery Dissection (SCAD) is a rare type of Acute Coronary Syndrome (ACS) that primarily affects younger individuals (under 65) who do not exhibit “traditional” cardiovascular risk factors such as dyslipidemia and hypertension. Previous genetic and epidemiologic studies indicate that connective tissue disorders (CTDs) such as Marfan and Loeys-Dietz syndromes as well as arteriopathies such as fibromuscular dysplasia (FMD) with known genetic causes are more prevalent among SCAD than other ACS patients. Each of these conditions, however, is associated with fewer than 0.5% of SCAD cases. Previous genetic studies of SCAD used CTD gene panels to screen for relevant mutations that segregate with SCAD in families based on currently accepted clinical genetics guidelines. Genetic diagnosis was achieved in only 8% of patients, likely due to the low penetrance and extreme genetic heterogeneity of SCAD. New approaches are needed to facilitate improved screening, diagnosis, treatment, and genetic counselling for SCAD patients.

Methods: We developed an analysis pipeline to identify potentially causal mutations without familial data based on minor allele frequencies, previously reported pathogenicity, and computational predictions of mutation intolerance. We tested our methodology on Whole Exome Sequencing data from 5 SCAD patients in the PRAXY-GENESIS cohort who had no traditional cardiovascular risk factors and were <51 years old, reasoning that these patients are the most likely to have an easily identifiable genetic cause such as a CTD.

Results: We identified strong candidate mutations in 3 patients. One is a missense mutation in the FBN1 gene, which encodes the fibrillin-1 protein. Mutations in this gene can cause Marfan syndrome. Another is a novel mutation in the LEMD3 gene, which encodes the inner nuclear envelope protein Man1, a repressor of the TGF-β pathway. Deletion mutations in this gene can cause the connective tissue disorder Buschke-Ollendorff syndrome and other TGF-β repressor mutations can cause Loeys-Dietz syndrome. The third identified mutation is a novel heterozygous frameshift mutation in BMP3, another protein that reportedly functions as a TGF-β repressor.

Conclusions: Our results demonstrate that monogenic disorders should be considered for SCAD patients, especially for early-onset cases without risk factors. Current clinical genetics practices often restrict analysis to previously implicated genes and require the analysis of entire families, however more comprehensive approaches such as the one tested in this work will soon allow for genetic diagnosis of low-penetrance, highly heterogeneous diseases with genetic data from only the affected individual.

Keywords: acute coronary syndrome, early onset, genetic epidemiology

γδ T CELLS MEDIATE αβ T CELL ACTIVATION IN ANGIOTENSIN II-INDUCED HYPERTENSION

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Objectives: Both innate and adaptive immune cells have been shown to play a role in hypertension and vascular injury. Recently, we demonstrated that a small subset of "innate-like" T lymphocytes, expressing the γδ T cell receptor (TCR) rather than the αβ TCR, plays a key role in hypertension and vascular injury. We demonstrated an increased number and activation (CD69+) of αβ and γδ T cells during the development of hypertension caused by angiotensin (Ang) II infusion, and that deficiency in γδ T cells prevented Ang II-induced hypertension, resistance artery endothelial dysfunction and spleen T-cell activation in mice. We hypothesized that γδ T cells mediate activation of other T cells in hypertension.

Methods: C57BL/6 male mice were infused with Ang II (490 ng/kg/min, SC) for 7 and 14 days (n=5-7). All mice were 14-15 week-old at the end of the study. Spleen T cell profile was determined by flow cytometry. γδ and αβ T cells were isolated using magnetic beads from peripheral lymph nodes and spleen from C57BL/6 male mice treated or not with Ang II for 14 days. αβ T cells were cultured alone or with γδ T cells (5:1) in presence of anti-CD3 antibodies plus or minus Ang II, and αβ T cell phenotype was evaluated by flow cytometry.

Results: Close correlations were demonstrated between the number (#) of activated CD69+γδ T cells and CD4+CD69+ T cells ($r^2=0.74$, $P<0.01$) and CD8+CD69+ T cells ($r^2=0.64$, $P<0.01$) after 7-day Ang II infusion. Correlations were also shown between the # of CD27+CD69+γδ T cells and CD4+CD69+ T cells ($r^2=0.76$, $P<0.001$) and CD8+CD69+ T cells ($r^2=0.65$, $P<0.01$) after 7-day Ang II infusion. In vitro, Ang II increased the fraction of CD69+αβ T cells when αβ T cells were co-cultured with γδ T cells isolated from control mice (% of αβ T cells: 19.9±2.9 vs. 16.4±2.6, $P<0.001$) but not when cultured alone. The fractions of CD69+ (% of CD69+αβ T cells: 35.7±2.7 vs. 18.9±1.5, $P<0.001$) and CCR6+ αβ T cells (% of CCR6+αβ T cells: 27.6±2.4 vs. 19.2±3.5, $P<0.05$) were increased when αβ T cells were co-cultured with γδ T cells isolated from Ang II-infused compared to control mice.

Conclusions: These results suggest that γδ T cells mediate activation of αβ T cells in Ang II-induced hypertension. Targeting γδ T cells may contribute to reduce the low-grade inflammation found in hypertension.

Keywords: γδ t cells, αβ t cells, t cell activation, hypertension, angiotensin II

Prediction of Rehabilitation Needs After Aortic Valve Replacement

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Background: Older adults undergoing transcatheter (TAVR) or surgical aortic valve replacement (SAVR) frequently cannot be discharged home because they are deconditioned and require rehabilitation. Clinical and geriatric predictors of post-procedural rehabilitation needs could be addressed to anticipate and prevent this disposition but they have yet to be examined in a multicenter study.

Methods: Post hoc analysis of a prospective cohort study from 14 hospitals in 3 countries. Patients ≥70 years of age were included if they underwent TAVR or SAVR and were discharged alive from hospital. Patients were excluded if they were discharged to a nursing home, other hospital, or hospice. The candidate predictor variables were: age, sex, body mass index, comorbidities, frailty as measured by the Essential Frailty Toolset (EFT), disability, depression, New York Heart Association (NYHA) class, left ventricular ejection fraction, predicted risk of mortality, procedure type, and complications. The outcome variable was discharge to a rehabilitation facility following the index hospitalization. Multivariable logistic regression and Bayesian model averaging were used to select a parsimonious model for future predictions.

Results: The cohort consisted of 1190 patients with a mean age of 81 ± 6 years. There were 758 TAVR and 432 SAVR, of which 136 (18%) and 78 (18%) were discharged to a rehabilitation facility. The final predictive model and score consisted of: advanced age (1 point if ≥80 years), sex (1 point if female), high NYHA class at baseline (1 point if class III/IV), high EFT score at baseline (1 point if ≥3), having a post-procedural complication (1 point), and undergoing a SAVR (1 point). The predicted risk of being discharged to a rehabilitation facility was 6%, 12%, 26%, 37%, or 51% if the rehab score was 0-1, 2, 3, 4, or 5-6 points, respectively. When prolonged length of stay was considered in the model, the effects of having a complication and undergoing a SAVR were attenuated and no longer significant.

Conclusion: A risk model for prediction of rehabilitation needs after TAVR and SAVR has been developed, and pending external validation, could be used to plan patients' post-procedural care and proactively select patients that may benefit from rehabilitation before their procedure (prehabilitation) rather than requiring it afterwards and not being fit for discharge to their home.

Keywords: rehabilitation, TAVR, SAVR

The Role of Memory Gamma Delta T Cells in Hypertension and Vascular Damage

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Hypertension, or high blood pressure, is the number one risk factor for disease burden and mortality worldwide. The immune system has been shown to play a role in the development of hypertension, and we recently demonstrated that a small subset of T cells, the “innate-like” γδ T cells, participate in the pathogenesis of the disease. γδ T cell depletion in mice resulted in a reduced ability of angiotensin II (Ang II) to induce hypertension and vascular injury. In addition, it has been shown that memory T cells develop during an initial hypertensive episode, sensitizing mice to develop hypertension to a second mild hypertensive challenge. Memory T cells express CD44 in mice and are subdivided into 3 categories: central memory T (TCM) cells that are CD62L+CCR7+ and are found in lymphoid organs, effector memory T (TEM) cells that are CD62L–CCR7– and are able to recirculate between lymphoid tissues, blood and peripheral organs, and tissue-resident memory T (TRM) cells that are CD62L–CCR7–CD69+CD103+ and reside in peripheral tissues. However, whether memory γδ T cells develop and play a role in hypertension remains unknown. We hypothesize that memory γδ T cells develop after an initial exposure to a hypertensive stimulus, and we aim to demonstrate that these cells are present after an initial hypertensive challenge. In order to do this, a flow cytometry panel was designed based on the expression of T cell memory markers. To maximize separation of positive and negative populations and minimize background noise, the panel needed to be optimized by titrating the fluorochrome-conjugated monoclonal antibodies using series of 8 dilutions of the antibody of interest, along with live dead staining and a second antibody to gate lymphocyte subsets. This was done using splenocytes collected from transgenic mice (ieET-1) made hypertensive by a 3-month induction of endothelium-restricted human endothelin-1 overexpression. We were able to find optimal antibody concentrations, and preliminary tests using a hypertensive ieET-1 mouse revealed the presence of γδ TCM and γδ TEM cell subsets in the spleen. This flow cytometry panel will allow us to show that memory γδ T cells develop after an initial exposure to a hypertensive stimulus, and that these cells are amplified after a second mild hypertensive challenge.

Keywords: hypertension, immune, memory, cardiovascular disease

A Trajectory Analysis of Daily Step Counts During a Physician-delivered Intervention in Adults with Type 2 Diabetes Mellitus and Hypertension

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Introduction: The integration of pedometers into clinical practice has the potential to enhance physical activity levels in patients with chronic disease. Our SMARTER randomized controlled trial demonstrated that a physician-delivered step count prescription strategy has measurable effects on daily steps, glycemic control, and insulin resistance in overweight patients with type 2 diabetes (T2DM) and/or hypertension. Given the benefits of the SMARTER strategy, we aimed to evaluate the patterns of step count change during the intervention, and the factors that influencing different responses.

Methods: The present analysis includes SMARTER trial active group participants who returned their step logbooks with recordings of daily step counts for 1-year (N=118/137). Group-based trajectory modeling (GBTM) was used to identify groups that follow statistically similar trajectories over time. We examined trajectories of mean steps/day by 30-day periods over 1-year, as well as the mean change from baseline for each 30-day period. Cumulative logistic regression models were used to identify predictors of group membership, including age, sex, body mass index (BMI), ethnicity, education, presence of T2DM, season start, and cardiorespiratory fitness (VO_2 peak).

Results: We identified 4 distinct trajectories of mean steps over 1-year. Participants with T2DM were 3.7 times (95%CI 1.7, 7.7) more likely to be in a less active step count trajectory compared to those without T2DM. Similarly, participants who were older were more likely to be in a less active step count trajectory: for a 10-year increase in age, the odds of being in the sedentary trajectory was 2 times (95%CI 1.3, 2.8) larger than being in the more active trajectories. When evaluating trajectories of step count change from baseline, the model yielding the best fit consisted of 3 distinct trajectory groups: (1) gradual decrease (2) gradual increase and (3) peaked increase. Participants who started the intervention in the spring and summer were 6.5 times (95%CI 2.8, 14.9) more likely to be in the decreasing trajectory, compared to the increasing trajectories. Age, presence of T2DM, BMI, ethnicity or education were not associated with trajectory membership. Unfortunately, we were underpowered to look at differences in health outcomes across trajectories.

Conclusions: Our findings support existing evidence of lower physical activity levels in older individuals and those with T2DM; however, the response to the step count intervention was not different. Season does impact the trajectory of step count change, which should be a consideration by physicians when starting step count prescriptions and setting targets for patients.

Keywords: Type 2 Diabetes Mellitus, Hypertension, Physical Activity Intervention, Step Count Trajectories, Group-Based Trajectory Modeling

Is a Recent History of Preeclampsia Associated with Increased Arterial Stiffness?

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Background: Preeclampsia (PE) is a severe disorder of pregnancy defined by de novo hypertension (>140/90mmHg) and proteinuria. It is the leading cause of maternal-fetal morbidity and mortality worldwide, including in North America. Relevant to this study, in the 10-14 years following a PE pregnancy, women demonstrate a higher incidence of cardiovascular diseases. However, the mechanisms contributing to this cardiovascular dysregulation are not fully understood. Therefore, the purpose of this study was to evaluate direct measurements of arterial stiffness and vascular measures which influence arterial stiffness in women who recently experienced a PE pregnancy.

Methods: We recruited 24 women who were 6-24 months postpartum (PE: n=12, age=34±6yrs, BMI=32±6kg/m^2), including control subjects with a recent history of a healthy pregnancy and no history of disordered pregnancies (Control: n=12, age=29±3ys, BMI=32±6kg/m^2). All subjects were without overt cardiovascular disease. Subjects were tested in the supine position following an overnight fast, and after abstaining from caffeine, strenuous exercise, and alcohol for 12 hrs. Central and peripheral arterial stiffness were quantified using carotid-femoral and carotid-finger pulse wave velocity (PWV), respectively. Mean arterial pressure (MAP) and cardiac output (Q) were measured beat-by-beat using finger photoplethysmography (Finometer Pro). Integrated muscle sympathetic nerve activity (MSNA) was measured from the peroneal nerve using microneurography. Total peripheral resistance (TPR; MAP/Q) and MSNA burst incidence (bursts/100 heartbeats) were used to quantify neurovascular transduction (TPR/MSNA), all of which contribute to arterial stiffness.

Results: Both central and peripheral PWV were higher in PE compared to controls (7.1±1.1 vs 6.0±0.7 m/s, P=0.01 and 7.6±0.8 vs 6.9±0.5 m/s, P=0.04, respectively). MSNA burst incidence was higher in the PE group (30±10 vs 19±9 bursts/100hb, P=0.04). However, MAP, Q, and TPR were similar between PE and controls (94±11 vs 89±9mmHg, P=0.2; 7.9±2.4 vs 6.8±1.1 L/min, P=0.2; 13±3 vs 13±2 mmHg/L/min, P=0.9). As such, we observed a trend towards reduced neurovascular transduction in PE relative to controls (0.46±0.2 vs 0.91±0.6 mmHg/L/min/bursts/100hb, P=0.1).

Conclusion: These data indicate that a recent history of a PE pregnancy is associated with increased arterial stiffness. However, it is unclear whether elevated MSNA plays a role in this increased stiffness, as we observed blunted neurovascular transduction in women who had PE. This blunting is indicative of the presence of “healthy” vascular mechanisms which offset the

Keywords: preeclampsia, arterial stiffness, sympathetic nerve activity, neurovascular transduction

The BP-MOM Study: Breastfeeding and blood Pressure patterns in MOthers with recent hypertensive coMplications of pregnancy

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Background: Hypertensive disorders of pregnancy (HDP) complicate approximately 5% of pregnancies and increase the risk of developing cardiovascular diseases (CVD). Women with HDP are less likely to initiate and continue breastfeeding due to specific biological, psychosocial, and contextual factors. However, the factors underlying breastfeeding outcomes in HDP women are not well described. As an example, an inflammatory milieu – more common in women with hypertension – may contribute to reduced milk supply through moderation of the stress response.
In addition to child health benefits, breastfeeding may lead to reduction of maternal blood pressure and future CVD risk. Breastfeeding interventions may thus be particularly beneficial for women with HDP. Accordingly, we are conducting a single-center randomized open-label pilot study to examine the feasibility of a nurse-led breastfeeding self-efficacy enhancing intervention among postpartum women with HDP. Based on the findings from this study, we are planning a multi-centre trial addressing biological and psychosocial differences between HDP and non-HDP breastfeeding women and assessing whether differential patterns in biomarkers contribute to differences in breastfeeding outcomes between these two groups.

Method: For the pilot study, we will recruit and follow 75 women with gestational hypertension or pre-eclampsia from delivery through one year postpartum. Participants are randomized to receive a nurse-led breastfeeding intervention or usual postpartum care. Study feasibility measures include recruitment rates, retention rates and participant satisfaction with the intervention. Other exploratory outcomes include infant feeding practices, maternal blood pressure, and results from a metabolic panel.
The multi-centre study will include both women with HDP and normotensive women. Plasma androgens, prolactin, human placental lactogen, oxytocin, and cortisol will be measured in relationship to a feed, in addition to a basic biochemistry and metabolic panel. Finally, blood samples will be stored in a biobank for future analyses.

Results: Recruitment for the pilot began in January 2019. Ten participants have been recruited to date. Challenges encountered thus far include coordinating recruitment activities with clinical staff schedules, generating interest in research participation among pregnant women, and recruiting at a high-risk urban medical center that regularly cares for patients living in remote regions.

Conclusion: The ongoing BP-MOM pilot study will serve to inform the need for and design of a large-scale RCT and biobank. Findings from this research are expected to be: 1) highly relevant to healthcare providers caring for women with HDP; and 2) generalizable to other postpartum clinics providing care for this vulnerable population.

Keywords: breastfeeding, hypertensive disorders of pregnancy, cardiovascular risk

Partial ablation of PDGFRa expressing cells is sufficient to increase atherosclerosis

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Background: Atherosclerosis is characterized by the accumulation of lipids, cells and fibers in the arterial wall. Atherosclerotic plaques tend to form in regions of low blood flow, whereas vessels exposed to high blood flow remain lesion-free. We created a surgical mouse model, arteriovenous fistula (AVF), which increases blood flow locally in the brachiocephalic artery (BCA), for the study of plaques specifically in this vascular segment. We found that high blood flow leads to a significant ~50% regression of BCA plaque size in AVF mice. FACS analysis revealed a significant increase in the total number of PDGFRa+ cells in the BCA plaques of AVF vs Sham control mice ($p<0.01$ at 7 and $p<0.05$ at 14 days post-surgery). No such changes were observed in the plaques of the aortic sinus. Therefore, we hypothesized that PDGFRa expressing cells regulate atherogenesis.

Methods: To investigate the role of PDGFRa+ cells in atherosclerotic plaque development, we generated a conditional LDLr-/- Pdgfra CreERT2+/-:DTR model (referred to as CRE+ mice hereafter). In this model, PDGFRa expressing cells are rendered selectively sensitive to exogenously administered diphtheria toxin (DT) by targeted expression of the DT receptor (DTR) following tamoxifen. CRE+ mice and CRE- littermates (CreERT2-/-:DTR) were placed for 9 weeks on a high fat diet (HFD) and were injected with DT (3 times weekly). Plaque size was evaluated with oil red O staining.
In parallel, to follow PDGFRa+ cells and their lineage during plaque development, we developed a conditional LDLr-/- Pdgfra CreERT2+/-:Rosa-tdTomato mouse model.

Results: Western blot analysis revealed a significant reduction (25%) of PDGFRa protein in the aortas of CRE+ vs CRE- mice. Furthermore, CRE+ mice displayed a significant greater lesion size compared with CRE- littermates (0.24 ± 0.015 vs 0.14 ± 0.009mm2). There were no significant differences in body weight, total white blood cells or lipid levels.
Concurrently, cells of the PDGFRa Tomato+ lineage were found within early atherosclerotic lesions (week 3 of HFD), and localized specifically in the cap and the media/plaque interface at week 9 of HFD. Most of these cells were positive for a-SMA, a smooth muscle cell marker.

Conclusion: PDGFRa expression was originally known for its deleterious role in vascular remodeling diseases and in cancer due to its association with mitogenic responses. More recently, it has been identified as a pan-mesenchymal progenitor cell marker. Our data suggest an unexpected, protective role for the PDGFRa expressing cell population in atherosclerotic plaque development.

Keywords: atherosclerosis, PDGFRa, mesenchymal cell population

VCAM-1 Targeted Poly(β-Amino Ester) Nanoparticles for Gene Delivery Under Flow and to the Endothelium

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The vascular endothelium is a vital barrier organ whose dysfunction has been implicated in diseases with high mortality and societal burden such as cancer and cardiovascular disease. Thus, great efforts are being made to devise novel and creative strategies to target the endothelium. Here, we focus on atherosclerosis, a chronic inflammatory disorder that can lead to heart attack or stroke. Atherosclerosis arises from lipid-laden deposits known as plaques that develop over time in branched or curved segments of the blood vessels that experience abnormal shear stress. Endothelial cells in these regions overlie the growing plaques and overexpress vascular cell adhesion molecule-1 (VCAM-1). Thus, we have developed a targeted nanoparticle for anti-inflammatory gene delivery purposes within the context of atherosclerosis. The particle is composed of a poly(β-amino ester) polymer or PBAE coupled with plasmid DNA encoding the anti-inflammatory cytokine IL-10. The main objective of this study was to determine if PBAE nanoparticles coated with or without a peptide specific for VCAM-1 could localize to inflamed endothelial cells and if nanoparticle uptake is affected by physiological flow and/or inflammation. We first pre-treated primary mouse endothelial cells (mECs) with TNF-a to increase expression of VCAM-1. We found that ~90% of activated mECs took up NPs (both coated and uncoated) under static conditions whereas only about 5% of non-activated mECs took up NPs. This result was mimicked under physiological flow in a microfluidic chamber slide. Thus, the coating does not interfere with particle uptake but there was non-specific binding and uptake with the uncoated particles. We used surface plasmon resonance with imaging (SPRi) biosensing to investigate the binding of NPs to the VCAM-1 protein alone coated on the sensor surface. This provided better insight into binding dynamics and showed that coated NPs stayed bound to VCAM-1 longer than uncoated ones. Finally we incubated NPs on cryo-sectioned aortic sinus samples from an atherosclerotic mouse model (LDLR-/- mice on high fat diet for 12 weeks). Here too, we discovered noticeable differences in binding of coated vs. uncoated particles to the endothelium overlying the plaque. Taken together, our data indicate that we can achieve binding and uptake of gene delivery NPs in inflamed primary endothelial cells but that there is also significant non-specific binding. Furthermore, coated NPs bind the VCAM-1 protein longer and were more specific for the inflamed endothelial cells lining atherosclerotic plaques.

Keywords: biomaterials, gene delivery, nanoparticles, atherosclerosis

Frailty Assessment in Older Adults Undergoing Interventions for Peripheral Arterial Disease

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Objectives: Frailty is a pivotal part of the preoperative evaluation and therapeutic decision making in older adults with peripheral arterial disease (PAD) since patient frailty is related to postoperative morbidity and mortality. However, performance-based frailty scales may not be feasible in this mobility-impaired population. The objective of this study was to determine the prevalence of frailty in this population and compare the incremental value of 6 questionnaire-based frailty scales to predict poor outcomes following interventions for PAD.

Methods: FRailty Assessment In Lower Extremity arterial Disease (FRAILED) was a prospective cohort study including 2 centers in Montreal, Canada, designed to examine frailty in patients with PAD. Consecutive patients undergoing endovascular or open interventions for PAD (Rutherford class 3 or higher) were enrolled. The prevalence of frailty was assessed in all patients using the following frailty scales: Edmonton Frailty Scale (EFS), FRAIL scale, Groningen Frailty Indicator (GFI), Modified Frailty Index (mFI), Multidimensional Prognostic Index (MPI), and the modified Essential Frailty Toolset (mEFT). The primary outcome was a composite of all-cause mortality and morbidity, including major vascular complication requiring surgical or medical intervention.

Results: The cohort consisted of 149 older adults with a mean age of 70.5±10.8 years. Patients with claudication and critical ischemia accounted for 40% (N=60) and 60% (N=89) respectively. Fifty-four percent (N=81) received endovascular interventions and 46% (N=68) received open interventions. Depending on the scale, the prevalence of frailty ranged from 37% to 70%. The incidence of all-cause mortality was 6.3% in the cohort over a median follow-up of 1.3 years. After adjusting for age, sex, predicted operative risk with the revised cardiac risk index (RCRI), diagnosis, and procedure type, the frailty scales with the greatest incremental value for mortality and morbidity were found to be the GFI (standardized adjusted OR 3.22, 95% CI 1.32 to 8.86, BIC 88.7) or the mEFT (standardized adjusted OR 1.99, 95% CI 1.01 to 3.97, BIC 93.2). The four other frailty scales were not statistically significant in the multivariable logistic models.

Conclusions: The prevalence of frailty and the prognostic impact of frailty varied depending on the scale used. The GFI and mEFT performed well and were most predictive of mortality and morbidity in patients with PAD undergoing interventions. The GFI and mEFT would be more appropriate to use in clinical practice when assessing frailty in patients with PAD.

Keywords: frailty, vascular surgery, epidemiology, peripheral artery disease

Inhibition of eIF4E phosphorylation regulates atherosclerotic plaque composition and development.

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Background: Eukaryotic initiation factor 4E (eIF4E) plays a key role in the initiation of translation. eIF4E is regulated by phosphorylation on Ser209 by MAP kinase-interacting serine/threonine kinases 1/2 (MNK1/2), downstream of p38/ERK1/2. Recent studies showed that eIF4E phosphorylation controls the translation of several factors, including chemokines metalloproteinases, and growth factors, which may regulate inflammation. Since atherosclerosis is a chronic inflammatory disease, we investigated the role of eIF4E activation in atherogenesis.

Methods: LDL receptor knock-out (ldlr-/-) mice were placed on a high fat diet (HFD) for 9 weeks and concurrently treated with a selective MNK1/2 inhibitor (SEL201) or vehicle. In parallel, LDLr-/- mice were crossed with eIF4ES209A/S209A knock-in mice displaying defective eIF4E phosphorylation (4Eki), and fed a HFD for 9 or 18 weeks. Another group of LDLr-/- mice were lethally irradiated and reconstituted with 4Eki bone marrow prior receiving HFD for 9 or 18 weeks.
Atherosclerotic plaque size was measured using oil Red O, and collagen (Sirius red), smooth muscle cell (alpha smooth muscle actin) and macrophage (CD68) contents evaluated by immunohistochemistry.

Results: No difference was observed in atherosclerotic plaque size or plaque SMC content between SEL201- and vehicle-treated mice, or between 9 week HFD 4Eki and WT littermates. However, plaque macrophage content was decreased by 39% in 9 week HFD 4Eki vs WT mice ($p<0.01$). Also, SEL201-treated and 9 week HFD 4Eki mice displayed a significant increase (24 and 40% respectively) in plaque collagen content, suggesting more stable plaques at early time points. Interestingly, 18 week HFD 4Eki mice developed smaller plaques (0.65 ± 0.05 vs 0.85 ± 0.05mm2, $p<0.01$) than WT littermates. However, no differences in plaque composition were observed at this time point.
4Eki BM transplantation did not have any effect on atherosclerotic plaque size or composition, at either 9 or 18 weeks HFD, suggesting that vascular rather than bone marrow-derived cells account for the protective effects of eIF4Eki and SEL201.
In vitro, SMCs from 4Eki mice were less prone to oxidized-LDL-induced apoptosis than WT SMCs (Annexin/PI). Moreover, basal proliferation rate of 4Eki SMCs was greater than WT SMCs, but unlike WT SMCs they did not further proliferate in response to oxidized-LDL (Ki67).

Conclusions: These data indicate that preventing eIF4E phosphorylation improves plaque stability in the short term and reduces plaque growth at long term. This occurs independently from myeloid/lymphoid cells. Our results suggest that eIF4E phosphorylation may play a key role in the regulation of SMC function within the atherosclerotic plaque.

Keywords: atherosclerosis, eIF4E, vascular smooth muscle cells, collagen

Renal Protection of Percutaneous Left Ventricular Assist Devices in High-Risk Percutaneous Coronary Intervention: A Systematic Review

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Background: The volume of complex high-risk percutaneous coronary interventions (PCI) is rising due to advancements in wire, stent, and catheter technologies. Acute kidney injury (AKI) due to PCI is independently associated with morbidity and mortality and has been reported in 7% of all-comer PCI cases and almost 20% in patients presenting with acute heart failure. The role of partial hemodynamic support with a percutaneous left ventricular assist device (LVAD) for renal protection in high-risk PCI in non-cardiogenic shock patients remains unclear.

Methods: We searched Medline, EMBASE, the Cochrane Library and Web of Science for studies that evaluated the use of temporary LVADs, such as the Impella 2.5, CP or 5.0 devices, in high-risk, non-cardiogenic shock patients undergoing PCI (aka "protected PCI"). Studies with less <10 patients were excluded. The definition of AKI was extracted from included studies.

Results: There were 3,454 potentially relevant publications, of which 10 studies were included in the analysis: 1 randomized controlled trial (n=226) and 9 observational studies (n=1,441). The definition of AKI in the studies was heterogeneous. One study used the Acute Kidney Injury Network criteria for AKI. The other studies defined AKI variably ranging from "change in kidney function," increase in creatinine by 50% and increase in creatinine more than two times from baseline. The incidence of AKI ranged between the studies from 0 to 15.4% (mean incidence of 5.2%). In patients with low left ventricular ejection fraction (one randomized controlled trial and eight observational studies (n=1,173)), the incidence of AKI ranged from 0 to 15.4% (mean incidence of 5.3%). Patients with preserved left ventricular ejection fraction (n=258) had a mean AKI incidence of 3.9%.

Conclusion: The impact of renal protective effects of temporary LVADs is uncertain due to the heterogeneity in reporting renal outcomes and the lack of larger randomized studies. There is a need for more rigour in defining and reporting renal outcomes and population characteristics in patients undergoing protected PCI.

Keywords: impella, renal, kidney, high-risk

A Comparison of angiotensin receptor-neprilysin inhibitor (ARNI) versus angiotensin inhibitors on the burden of arrhythmias in patients with stablized HFrEF under continuous implantable defibrillator monitoring

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Background: Sacubitril/valsartan reduces all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF). Atrial and ventricular tachyarrhythmias frequently coexist with HF-rEF. The purpose of this study is to determine if salcubitril/valsartan is associated with less arrhythmias in HFrEF patients compared to ACEIs.

Method: This is a retrospective cohort study. Data was collected from the Heart Failure clinic at a tertiary-care hospital. Eligible patients were those with at least a two-year history of HFrEF, EF<=40%, NYHA≥II, who had received ACEI or ARBS and had an ICD for at least one year before switching to sacubitril/valsartan. Data collected for 1 year before and 1 year after starting sacubitril/valsartan.

Result: Of 384 patients on an angiotensin receptor-neprilysin inhibitor who were screened, 68 consecutive eligible patients were eligible and analyzed. Mean age was 65.9±11.4years, 32.3% were women and 58.8% had ischemic cardiomyopathy with a mean EF of 24.1%±8.2%. After one treatment with sacubitril/valsartan, the mean EF was 27.2%±11.0%. There was a significant reduction in the total number of atrial arrhythmias experienced after starting sacubitril/valsartan (499 episodes versus 672 episodes; P<0.01) but not in the number of ventricular arrhythmia episodes. No significant difference in the proportion of patients who experienced ventricular arrhythmias before and after treatment with sacubitril/valsartan (50% versus 56%) was found.

Conclusions: In this optimally cohort of HFrEF patients with a low incidence of arrhythmias, sacubitril/valsartan did not decrease the incidence of ventricular arrhythmias but was associated with a decrease in the total number of episodes of atrial arrhythmias. Larger studies are needed to confirm these findings, particularly in populations with higher incidences of ventricular arrhythmias.

Keywords: arrhythmia, ARNI, HFrFH

Lipoprotein(a) as a Risk Factor for Calcific Aortic Valve Disease Across Ethnicities

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Background: Calcific aortic valve disease (CAVD) is a disorder involving calcification and thickening of the heart's aortic valve. Recent studies in European populations have implicated genetic variation at the LPA locus in the development of CAVD, highlighting elevated lipoprotein(a) (Lp[a]) levels as an important risk factor. It is not clear whether genetic risk factors for elevated Lp(a) and CAVD in Europeans are transferable across ethnicities.

Methods: We examined whether LPA variants rs10455872 and rs3798220 were associated with Lp(a) levels and aortic valve calcium (AVC) in 1,581 African-Americans and 1,324 Latin-Americans from the Multi-Ethnic Study of Atherosclerosis (MESA). We also examined whether proportion of African ancestry, as estimated by genetic markers, was associated with Lp(a) levels. All models were adjusted for age and sex, and Lp(a) levels were natural log transformed.

Results: Each minor allele of rs10455872 was associated with increased Lp(a) levels in African-Americans (ln[nmol/L] [95% CI], 1.21 [0.75,1.70]; p=2.5e-07) and Latin-Americans (2.04 [1.60,2.40]; p=2.8e-23). Similarly, rs10455872 was associated with greater odds of AVC in African-Americans (OR [95% CI], 2.67 [1.12,6.40]; p=0.028) and Latin-Americans (2.20 [1.06,4.58]; p=0.035). Conversely, rs3798220 was not associated with AVC in either ethnicity (p>0.05) and was associated with a decrease in Lp(a) levels in Latin-Americans (-0.41 [-0.55,-0.28]; p=3.0e-09). A greater proportion of African ancestry was associated with increased Lp(a) levels in both African-Americans (ln[nmol/L] per 10% increase [95% CI], 0.065 [0.036,0.095]; p=1.5e-05) and Latin-Americans (0.13 [0.095,0.17]; p=6.6e-12).

Conclusions: Genetic risk factors for elevated Lp(a) and CAVD demonstrate ethnicity-specific associations. In addition, ancestry may contribute to elevated Lp(a) levels. Further research is needed to understand how other risk factors for CAVD differ in non-European populations.

Keywords: lipoprotein(a), calcific aortic valve disease, genetic risk factor, non-european population

Sarcopenia in Older Adults Undergoing Cardiac Surgery

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Background: Sarcopenia, defined as age-related loss of muscle mass and strength, is one of the biological hallmarks of frailty. In practice, muscle mass is typically measured using a dual x-ray absorptiometry (DXA) scan, while strength is measured using physical performance tests. However, DXA may be less accurate in acute cardiac patients due to the confounding effect of body edema, and strength alone may be a superior indicator of muscle quality in aging.

Methods: A convenience sample of older adults referred for cardiac surgery were prospectively consented and enrolled at the Jewish General Hospital. After a structured questionnaire and physical performance battery, patients underwent a DXA scan (GE Lunar) to measure their appendicular muscle mass (AMM) – the sum of fat-free tissue in their arms and legs. Patients were categorized as sarcopenic based on the European Working Group guidelines if they had low AMM and low strength as measured by the timed chair rise test >15 seconds. Both non-indexed and height-squared-indexed cutoffs were explored for low AMM. A Cox proportional hazards model was used to test the association between sarcopenia (or its individual components) and all-cause mortality adjusting for age, sex, and cardiac surgery type.

Results: The cohort consisted of 134 patients with a mean age of 70.7 ± 10.2 years and 23% female. The cardiac surgery type was isolated coronary bypass in 58%, valve surgery in 30%, and decision not to proceed with surgery in 12%. The mean AMM was 24.2 ± 5.1 kg in men and 21.0 ± 5.2 kg in women. The prevalence of sarcopenia was 10% and 13% using non-indexed and indexed cutoffs, respectively, similar in men and women. In the multivariable model, sarcopenia was not associated with mortality (N=24) over 2 years of follow-up, and neither was AMM alone. Timed chair rise time alone was associated with mortality as a continuous variable and a dichotomous >15 second variable (HR 7.72, 95% CI 1.75 to 34.11).

Conclusion: Lower-extremity muscle strength is more predictive than muscle mass or DXA-based sarcopenia in predicting survival after cardiac surgery.

Keywords: sarcopenia, frailty, older adults

Differences in the Effects of Clopidogrel Between Women and Men: A Genetic Approach

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Background: Young women experiencing an acute coronary syndrome (ACS) have poorer health outcomes than men. Sex and polymorphisms in genes coding for drug metabolism enzymes [cytochrome P450 (CYP)] could be implicated as they are independent factors for variability in response to antiplatelet agents such as clopidogrel. However, the role of gene-sex interactions and clinical outcomes has not been extensively explored.

Objectives: To determine whether sex interactions exist with the variants of CYP genes among users of clopidogrel in relation with thrombotic and bleeding risk.

Methods: We tested genotypes for nine CYP variants for young acute myocardial infarction (AMI) patients (aged 18-55 years) from the GENESIS-PRAXY (GENdEr and Sex DetermInantS of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary SYndrome) and VIRGO (Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients) cohorts. A Genetic Risk Score (GRS) for CYP alleles was calculated. We explored sex differences in thrombotic risk, as well as bleeding risk, by investigating sex-gene interactions with clopidogrel at the time of presentation and discharge from AMI respectively.

Results: The case-only analysis for clopidogrel users at time of AMI onset (n=164) showed that thrombotic risk was greater in female carriers of CYP2C9*3 LOF allele (OR=2.6, 95% CI=1.13-6.06, p=.02). A sex-based comparison of the GRS showed that young women had a higher mean score (2.12±1.02) as compared to men (2.04±1.07) though not significant. There was no association between the gain of function variant (CYP2C9*17) and bleeding risk in clopidogrel users at discharge (n=481) regardless of sex.

Conclusion: CYP2C9*3 allele confers a higher risk of AMI in young women likely explained by a higher on-clopidogrel platelet reactivity. Sex differences in drug response should be explored to improve drug safety and efficacy.

Keywords: clopidogrel, pharmacogenetics, cytochrome P-450, genotype, acute coronary syndrome

Characterization of exosomes derived from amniotic stromal cells and their applications for cardiac repair and rejuvenation

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Background: Stem cell therapies for tissue regeneration after myocardial infarction (MI) has been investigated for over 20 years, but even after dozens of clinical trials, there is still no standard therapy for patients. Recently, extracellular vesicles from stem cell sources have been investigated as a novel therapeutic strategy for patients undergoing an MI, however the mechanisms by which these vesicles promote regeneration is poorly understood. Here, we show that exosomes isolated from amniotic stromal mesenchymal stem cells (ASCs) promote cytoprotection and regeneration, which may be mediated in part by Wnt-signaling.

Methods: Vesicles were isolated from ASCs via ultrafiltration and ultracentrifugation. Vesicles were characterized using transmission electron microscopy, Nanosight analysis and proteomic profiling. Ischemic injury was induced in cardiac endothelial cells (CECs) using a hypoxic incubator and functional changes was assessed via changes in proliferation, migration and metabolic activity. Differentiation of ASCs was assessed via Western blotting, immunocytochemistry and RTPCR.

Results: ASCs secrete small exosome-like vesicles that are 50-150nm in diameter. Proteomics analysis revealed that hypoxic preconditioned ASCs secrete more proteins involved in anti-inflammation, anti-apoptosis and cytoprotection. One particular molecular pathway identified was Wnt-signalling. Exosome treated-CECs promoted cytoprotection and increased proliferation and migration. Independent activation of Wnt signaling in these cells via treatment with Wnt5a and Wnt11 had similar effects. Furthermore, Wnt-treated ASCs promoted cardiogenesis through increased protein and mRNA expression of cardiac markers and changes in metabolic activity that resembles early cardiomyoctes.

Conclusions: Here, we provide insight into some of the mechanisms involved in exosome-mediated cardiac repair and rejuvenation. Together, these results show that exosomes from ASCs may be a novel therapeutic strategy for cardiac regeneration after MI and that independent activation of Wnt-signaling may produce similar regenerative effects.

Keywords: myocardial infarction, stem cells, extracellular vesicles, wnt signaling, regerenation

Echocardiographic Characteristics of Heart Failure Patients with Severe Tricuspid Regurgitation.

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Introduction: The proportion of patients with heart failure (HF) and severe tricuspid regurgitation (TR) that are potential candidates for a percutaneous tricuspid valve intervention is unknown. The aim of this study was to evaluate in a real-world setting the echocardiographic characteristics of Heart Failure HF patients with severe TR.

Methods: This was a retrospective cohort study of 2133 adult patients enrolled in the HF clinic at the McGill University Health Center from 2007 to 2017, totaling 10 300 echocardiograms. Included in our study were patients with a clinical diagnosis of HF and available echocardiographic follow up. All data after heart transplant or ventricular assist device was excluded. The severity of TR was classified according to the American Society of Echocardiography guidelines. All patients who never had severe TR during their follow-up were included in the control group.

Results: There were 321 patients with severe TR at any time during the follow-up period (mean age 66±16 years; 61% male), whereas 1812 patients did not have severe TR (mean age 60±15 years; 60% male). Among patients with severe TR, left ventricular ejection fraction (LVEF) was low (≤50%) in 76%, compared to the control group in which LVEF was low in 71% ($p=0.07$). Severe mitral regurgitation (MR) was present in 26% of the severe TR group compared to 5% in the the control group ($p<0.0001$). Moreover, elevated pulmonary artery systolic pressure (PASP) (>50mmHg) was present in 53% of the severe TR group, compared to 20% in control group ($p<0.0001$). Moderate and severe right ventricular (RV) systolic dysfunction were present in 34% and 12% of the severe TR group, respectively. However, in controls moderate and severe RV dysfunction was present in only 10% and 2%, respectively ($p<0.0001$). Finally, severe RV dilatation was present in 28% and moderate RV dilatation in 33% of the severe TR groups as compared to the control group with 3% with severe dilatation and 6% with moderate RV dilatation ($p<0.0001$).
Approximately 50% of patients with severe TR had less than moderate RV dilatation and systolic dysfunction. This subgroup could be eligible for a tricuspid valve intervention.

Conclusion: In patients with HF, severe TR is associated with worse echocardiographic parameters including severe MR, pulmonary hypertension, RV dilatation and RV systolic dysfunction. Half of patients with severe TR could be eligible for tricuspid valve intervention.

Keywords: heart failure, severe tricuspid regurgitation, intervention

Methodological Considerations for the Measurement of Arterial Stiffness using Applanation Tonometry

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Introduction: Accurate comparisons of cfPWV within and across studies requires that standardized procedures be followed. Guidelines suggest reporting the average of at least two measures. If the difference exceeds 0.5 m/s, a third measure should be taken, and the median value reported. However, in many published reports, duplicate measures are averaged irrespective of the distance between values. Alternatively, another accepted method involves repeating measures until two values are within 0.5 m/s (the method we have applied in all of our studies). We aimed to evaluate the impact of these methods on the reported cfPWV value.

Methods: Measurements of cfPWV (SphygmoCor system) were used from five existing studies, including participants spanning a wide age range, both men and women, and including co-morbid conditions, such as hypertension, T2DM, as well as women assessed during pregnancy. In participants with ≥3 high-quality measures, differences in the median value (MED) and 1) the average of first two measures (AVG1) and 2) average of two measures within 0.5 m/s (AVG2) were evaluated using paired T-tests and Bland-Altman plots.

Results: Participants' mean age was 51.1±14.8 years, and BMI was 27.8±5.9 kg/m2 (N=302, 80% women). The overall mean difference between MED and AVG1 was -0.10 (95% -0.17, -0.04) m/s. The absolute difference exceeded 0.5 m/s in 22% and 1 m/s in 8% of participants. The mean difference between MED and AVG2 was 0.11 (95% CI 0.05, 0.17) m/s. The absolute difference exceeded 0.5 m/s in 34% and 1 m/s in 8% of participants. Scatter around the bias line increased with higher mean values of cfPWV.

Conclusions: Although the overall mean difference between methods was not clinically relevant, large variation led to absolute differences that exceeded 0.5 m/s in a large proportion of participants. Researchers must be transparent in their reporting, and these methodological differences when measuring arterial stiffness should be considered when comparing different studies. Standardized protocols should be implemented in all studies.

Keywords: arterial stiffness, methodological considerations, applanation tonometry

Mortality Benefit of Alirocumab: a Bayesian Perspective

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Introduction: The publication of the ODYSSEY Outcomes trial demonstrated that the PCSK9 inhibitor (PCSK9i) alirocumab reduced major cardiovascular events. However, due to the hierarchical testing strategy utilized for the multiple outcomes examined, the observed reduction in all-cause mortality was labeled “nominally significant” which has clouded its interpretation.

Methods: We re-analyzed the data from the ODYSSEY Outcomes trial using Bayesian methods. To cover the range of varying prior probabilities, we generated various prior probabilities using mortality data from previous similar PCSK9i trials. We first used data from the ODYSSEY Outcomes trial with a non-informative prior, then sequentially added data from ODYSSEY Long Term and the FOURIER trial, giving FOURIER a 10% weight because it used evolocumab not alirocumab. Using partial weights allows for a statistical compromise: the prior data from FOURIER is not given full weight when applied to the current trial (since it used a different molecule) nor is it dismissed entirely. We then estimated the (posterior) probability of any mortality benefit, as well as the probability of a 1% and 0.5% mortality reduction on the absolute scale, equivalent to a number needed to treat (NNT) of 1 in 100 or 1 in 200, respectively.

Results: In the ODYSSEY outcomes trial, all-cause mortality was 3.5% for alirocumab vs. 4.1% for placebo. The posterior probability of a mortality reduction using only the ODYSSEY Outcomes data was HR 0.85 (95%CrI 0.74-0.99) which corresponded to a 98.4% probability of a mortality benefit. When the ODYSSEY Long Term data was added to the analysis, the posterior probability was HR 0.84 (95%CrI 0.72-0.97) with a 99.9% probability of mortality reduction, and when the FOURIER data was added to the analysis the posterior probability was HR 0.85 (95%CrI 0.74-0.98) with a 99.8% probability of a mortality reduction. The probability of a greater than 1% absolute risk reduction (ARR) ranged from 8% to 24%, while the probability of a greater than 0.5% ARR ranged from 66 to 89%.

Conclusion: This Bayesian analysis treats data as fixed, allows a direct examination of the mortality data without concerns for type 1 error, and allows the incorporation of prior data. It demonstrates a high likelihood that alirocumab confers a reduction in all-c *Dierick* ause mortality, despite the equivocal interpretation of the data in the original ODYSSEY Outcomes publication. When considering the data from both molecules on the market, the probability of a mortality reduction with PCSK9 inhibition remains high.

Keywords: cholesterol, PCSK9, bayesian, alirocumab

Machine Learning Derived Algorithms to Identify Patients with Congenital Heart Disease from Large Claims Databases

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Background: Identifying patients from large claims databases is becoming increasingly important for big data acquisition in health care research. Machine learning methods have the ability to extract sophisticated patterns of big data to predict outcomes without relying on many clinical assumptions. In this study, we aimed to derive efficient machine learning algorithms for identifying patients with congenital heart disease (CHD) using a large administrative database.

Methods: A database was assembled from merging the Quebec health service claims database, hospitalization records, and vital status database by unique patient identification numbers. It included longitudinal data from 61,386 patients with at least one CHD related diagnosis and/or surgical procedure between 1983 and 2000. Among them, 45,960 patients were labeled as true CHD patients by a tired hierarchical approach developed and validated through manual audits. Machine learning models for correct labeling the patients regarding their CHD diagnoses were developed and validated using supervised learning. We divided the whole patient cohort into two datasets: training set (80%) and test set (20%). Gradient Boosting Decision Tree (GBDT) and 5-fold cross-validation were adopted with the evaluation criteria of area under the receiver operating characteristic curve (AUC-ROC).

Results: We observed that the machine learning models could capture the interaction degrees of predictors and achieve high predicting performances, with an AUC-ROC around 0.97 for both the training and test sets. We also observed that the performance of the machine learning models remained stable in both the training and test datasets despite the complicated interactions between predictors in the database. Compared to conventional logistic regression model, GBDT algorithms showed hrobigher predicting performance with better AUC-ROC, F1-socre and accuracy respectively.

Conclusions: This study showed that machine learning methods could learn from data and make accurate predictions for CHD diagnosis using large claims databases. These findings suggest that machine learning methods can be considered as a reliable approach in clinical research for generating prediction models using administrative databases.

Keywords: machine learning, congenital heart disease, administrative database

miR-338-3p down-regulation caused up-regulation of alkaline ceramidase 2 and glutathione peroxidase 3 mRNAs in subcutaneous small arteries of hypertensive patients with chronic kidney disease

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Background: Hypertension (HTN) and chronic kidney disease (CKD) are two of the most prevalent global health conditions that cause millions of deaths per year. They are associated with vascular damage characterized by vascular remodeling and stiffening and endothelial dysfunction. miRNAs are a class of small non-coding RNA that regulate gene expression by binding to their target messenger RNAs (mRNAs), thereby leading to mRNA degradation or translational repression. Their implication in vascular injury remains unclear. We aimed to identify differentially expressed (DE) miRs in small arteries of HTN and CKD human subjects to gather insight into pathophysiological molecular mechanisms in these conditions.

Methods: Normotensive, HTN [systolic blood pressure (BP) >135 mmHg or diastolic BP of 85-115 mmHg with BpTRU] and CKD subjects (estimated glomerular filtration rate <60mL/min/m2) (n=15-16) were studied. Small arteries were isolated from subcutaneous gluteal biopsies and RNA extracted for small and total RNA sequencing using Illumina HiSeq-2500 and further studied using a systems biology approach. Differentially expressed (DE) genes were identified with fold change >1.5 and fold discovery rate <0.1.

Results: DE miRs were identified (P<0.05) uniquely associated with HTN (3↑ and 6↓) or CKD (42↑ and 39↓) or both groups (2↓). Correlation between RNA-sequencing and RT-qPCR data was demonstrated for 3 of 14 tested miRs. Among them, the first-ranked, miR-338-3p (r=0.91, P<10-16), uniquely associated with CKD, was further studied. miR-338-3p and some of its predicted targets were highly expressed in human aortic endothelial cells (HAECs). Two of them, alkaline ceramidase 2 (ACER2) and glutathione peroxidase 3 (GPX3), were up-regulated by ~36% and ~60% in HAECs transfected with anti-miR-338-3p, respectively (P<0.05). miR-338-3p mimic co-transfection decreased by 30% luciferase activity of reporter vectors containing the conserved wild-type but not mutated ACER2 or GPX3 3’ untranslated transcribed region miR-338-3p-5p binding sites (P<0.05).

Conclusion: miR-338-3p down-regulation was found in small arteries, uniquely associated with CKD. ACER2 and GPX3, which were identified as miR-338-3p targets, may play a role in vascular injury in CKD

Keywords: chronic kidney disease, hypertension, miRNAs, small arteries, vascular damage

Malnutrition and Mortality in Frail and Non-Frail Older Adults Undergoing Interventions for Peripheral Arterial Disease

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BACKGROUND: Older adults undergoing interventions for peripheral arterial disease (PAD) may be at risk for malnutrition. This study sought to determine the association between preprocedural nutritional status and all-cause mortality.

METHODS: This was a post-hoc analysis of the Frailty Assessment In Lower Extremity arterial Disease (FRAILED) prospective cohort including 2 centers recruiting patients between October 1st 2015 and August 1st 2016. Individuals who underwent vascular interventions for Rutherford class 3 or higher PAD were enrolled. The Mini Nutritional Assessment (MNA)-Short Form was assessed by trained observers preprocedure, with scores ≤7 of 14 considered malnourished and scores 8 to 11 of 14 considered at risk for malnutrition. The modified Essential Frailty Toolset (mEFT) was simultaneously assessed to measure frailty, with scores ≥3 of 5 considered frail. The primary endpoint was all-cause mortality at 12 months after the procedure. Multivariable logistic regression was used to adjust for potential confounders.

RESULTS: There were 148 subjects with 39.2% females, a mean age of 70 years, and a mean body mass index of 26.7 kg/m2. In the cohort, 59 (40%) had claudication and 89 (60%) had chronic limb threatening ischemia (CLTI) with 98 (66%) undergoing endovascular revascularization and 50 (34%) undergoing open or hybrid revascularization. Overall, 3% of subjects were classified as malnourished and 33% were at risk for malnutrition. There were 9 (6%) deaths at 12-months. Mini Nutritional Assessment-Short Form scores were modestly correlated with the mEFT scores (Pearson's R=-0.48, P<0.001). Patients with malnourishment or at risk of malnourishment had 2.5-fold higher crude 1-year mortality compared with those with normal nutritional status. In frail patients with mEFT scores ≥3 (41%), malnutrition was associated with all-cause mortality (adjusted OR: 2.08 per point decrease in MNA scores; 95% CI: 1.03 to 4.35); whereas in nonfrail patients with mEFT scores <3 (59%), MNA scores had no effect on mortality (adjusted OR: 1.05; 95% CI: 0.56 to 2.00).

CONCLUSIONS: Preprocedural nutritional status is associated with mortality in frail older adults undergoing interventions for PAD. Clinical trials are needed to determine whether pre- and postprocedural nutritional interventions can improve clinical outcomes in these vulnerable individuals.

Keywords: frailty, malnutrition, peripheral artery disease, mortality

A Longitudinal Analysis of Arterial Stiffness and Wave Reflection in Pre-eclampsia: Identification of Changepoints

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Background: Pre-eclampsia (PrE) is a leading hypertensive disorder of pregnancy. Identifying vascular dysfunction prior to PrE onset is critical for the development of effective early screening strategies.

Methods: In this prospective longitudinal study of women with singleton high-risk pregnancies, arterial stiffness and wave reflection parameters were assessed using applanation tonometry starting at 10-13 weeks and repeated every 4 weeks thereafter. Changepoints in carotid-femoral pulse wave velocity (cfPWV), carotid-radial PWV (crPWV), augmentation index (AIx), time to wave reflection (T1R), pulse pressure amplification (PPA), and subendocardial viability ratio (SEVR) were compared between women who did and did not develop PrE.

Results: A changepoint in cfPWV and crPWV was detected at 14-17 weeks. cfPWV then increased in women who developed PrE but decreased in women who did not; a 1.2 m/s difference in cfPWV between women who did and did not develop PrE was observed at 22-25 weeks' gestation. Conversely, crPWV converged in the two groups from a baseline difference of 1.05 m/s (95% CrI: 0.37, 1.72). No differences were observed in AIx between women who did and did not develop PrE, however, the former group demonstrated an increase in AIx at 18-21 weeks that was not seen in women who did not develop PrE until 30-33 weeks. No differing changepoints were observed between the two groups in T1R, PPA, nor SEVR.

Conclusions: Altered vascular adaptations in women with PrE were detected in early second trimester between women who did and did not subsequently develop PrE using measures of arterial stiffness and wave reflection. Our findings will inform continuing efforts to identify early PrE screening, monitoring, and therapeutic programs.

Keywords: arterial stiffness, preeclampsia, pulse wave velocity, changepoints, wave reflection

Clinical Biomarkers in Frailty Prediction

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Background: Frailty can be challenging to measure in acute cardiac patients who are often unfit to complete questionnaires and physical performance tests. We sought to explore clinically-available biomarkers that could be used to assess frailty in this setting.

Methods: We carried out an 8-month cross-sectional study (January to August 2018) in an inpatient cardiology unit. The biomarkers studied included clinically-indicated results from the complete blood count and biochemistry panel as well as C-reactive protein, NT-pro-BNP, and levels of vitamin B12, C, and 25-hydroxyvitamin D (25OHD). Frailty was ascertained by the Rockwood's Clinical Frailty Scale(CFS), handgrip strength, and bioimpedance phase angle. In addition, we calculated Rockwood's Frailty Index Lab score (FI-LAB) and InSilico's Aging.AI score. The association between these biomarkers and frailty measures was assessed by a Spearman correlation matrix.

Results: The cohort consisted of 138 patients with a median age of 73 years (IQR 64-85) and 52% females. The proportion of patients classified as frail was 27%, 40%, and 55%, according to the CFS, handgrip strength, and phase angle, respectively.The biomarkers that significantly correlated with two or more of these frailty measures were: NT-pro-BNP, blood urea nitrogen, creatinine, albumin, hemoglobin, and ferritin. Our biomarker score combining NT-pro-BNP, blood urea nitrogen, albumin and hemoglobin was correlated with all frailty measures (R 0.3-0.7, $P<0.001$), as were the FI-LAB and Aging-Ai scores. Hypovitaminosis was present in 33%, and 68% for vitamins C and D, respectively. Circulating vitamin C and 25OHD concentrations did not correlate with any of the frailty measures.

Conclusion: Clinically-available laboratory tests can be used to generate biomarker scores that are associated with frailty and feasible in acutely ill cardiac patients. Hypovitaminosis C and D were highly prevalent in this population, but their clinical implications are neither expressed nor indicated by frailty.

Keywords: acute cardiology, older adults, nutrition, frailty

Visual evidence of distinct intracellular itineraries of lipoprotein-cholesterol in hepatocytes

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Background. Atherosclerosis accounts for the majority of cardiovascular disease cases in the population and is caused by the deposition of cholesterol-enriched apolipoprotein B (apoB) lipoproteins in the arterial wall. Plasma levels of atherogenic apoB-lipoproteins are governed by the hepatocytes as they are the carrefour of cholesterol trafficking from both dietary- and endogenous lipoprotein sources. Early studies suggest that while dietary cholesterol is able to downregulate cholesterol biosynthesis in the liver, low-density lipoprotein (LDL)-derived cholesterol cannot. We hypothesize that LDL-derived cholesterol is exclusively shunted away from the cholesterol regulatory pool in hepatocytes, while dietary cholesterol in the form of chylomicron remnants (CRs) is able to regulate hepatic cholesterol homeostasis. Our goal is to provide biochemical and imaging evidence for these two independent pathways.

Methods. A combination of fluorescence imaging and biochemical experiments were performed in immortalized human hepatocytes (IHH). To study the fate of cholesterol from different lipoproteins, IHH were treated with LDL and CR loaded with 3H-cholesterol. Different lipid species were quantified by a scintillation counter. Immunofluorescence and live cell imaging were used to study the intracellular itineraries of LDL and CR in IHH cells. The lipophilic dyes DiO and DiD permitted imaging of LDL and CR in live hepatocytes.

Results. Our group has shown that in hepatocytes, LDL-derived cholesterol stimulates its esterification by acyl-CoA:cholesterol acyltransferase 2 (ACAT2) in the endoplasmic reticulum (ER) and increases its secretion within very-low density lipoprotein (VLDL). We have termed this the shunt pathway. Dietary cholesterol originating from CRs enters the plasma membrane and rapidly equilibrates with the cholesterol regulatory pool, preventing cholesterol biosynthesis and uptake. This preliminary biochemical evidence agrees with our visual evidence of the shunt pathway. ACAT2 was localized to perinuclear punctate domains suggesting specialized function. We observed that apoB and ACAT2 co-localize in these domains, reinforcing the role of ACAT2 in VLDL secretion. Finally, ACAT2 co-localizes with LDL-containing lysosomes in IHH, while CR-lysosomes were diffuse in the cytoplasm. Interestingly, treating IHH with an ACAT2 inhibitor appeared to cause the disappearance of punctate ACAT2. These results suggest ACAT2 clusters to generate specialized regions of function (SROFs) in the ER to promote VLDL secretion.

Conclusion. We provide visual and biochemical evidence showing that hepatocytes specifically direct LDL-cholesterol away from the regulatory pool, while CR-cholesterol decreases cholesterol synthesis and uptake. The results suggest a cycle whereby hepatic uptake of LDL-cholesterol is directly re-secreted as VLDL, thereby promoting atherosclerosis development.

Keywords: atherosclerosis, liver, low density lipoprotein, immunofluore science, ACAT2

Investigating the function of Rab18 in regulating cytosolic lipid droplet storage in C. elegans

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Background: The excessive storage of neutral lipids in lipids droplets (LDs) is a consequence of excess dietary nutrient uptake and the primary cause of major metabolic disorders, including obesity, diabetes, and atherosclerosis. Recent proteomic studies investigating the profile of proteins associated with the monolayer surface of LDs to yield insights into the complex regulation of fat storage and mobilization have identified Rab18. Rab18, a small GTPase protein localized on the surface of LDs, plays a key role in several LD-related processes, including lipogenesis, lipolysis, and lipophagy. Although Rab18 has been previously associated with multiple functions, ranging from the negative regulation of secretion in neuroendocrine cells to mediating the apposition of LDs to the ER, its fundamental function in lipid metabolism remains disputed.

Methods and Results: To elucidate the function of Rab18 on cytosolic LDs, we attempted to identify effectors of Rab18 by a proximity-dependent labeling approach. A BioID screen for GTPase-deficient Rab18(Q67L) proximate and interacting proteins identified TBC1D5, a Rab7 GTPase-activating protein (GAP). The acknowledged function of Rab7 GTPase as a positive regulator of hepatocellular lipophagy led us to hypothesize that Rab18 could function in the recruitment of TBC1D5 to the surface of LDs to inhibit Rab7-mediated lipophagy. To validate this hypothesis and further understand the function of Rab18 in regulating LD storage at the organismal level, we performed a quantitative assessment of fat levels in RAB-18 knockout C. elegans under both fed and fasted conditions using Nile Red (NR) staining. C. elegans carrying the rab-18 (ok2020) deletion exhibited a significant reduction in NR fluorescence intensity compared to wildtype (N2) worms under both fed and fasted (6 hours) conditions ($p<0.0001$). We proceeded to investigate the effect of rbg-3 (TBC1D5) knockout on overall fat levels in C. elegans using NR and Oil Red O (ORO) staining. rbg-3 mutants exhibited significantly reduced NR fluorescence and ORO staining intensities compared to N2 worms under fed conditions ($p<0.0001$ for NR and $p<0.001$ for ORO).

Conclusions: Our findings are in accordance with the proposed hypothesis as the deletion of rab-18 or rbg-3 in C. elegans is associated with a significant reduction in overall fat content, which could be attributed to the loss of inhibition of Rab7 by its GAP RBG-3 (TBC1D5) and the subsequent activation of Rab7 mediated lipophagy. Further investigation into the function of Rab18 in lipophagy may contribute to our understanding of the conserved regulation of fat storage and metabolism.

Keywords: lipid droplets, Rab18, lipid metabolism

Long-term Residual Risk and Predictors of Cardiovascular Disease in Individuals Taking Statins for Primary Prevention: Insights from the Cartagene Study

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Background: The efficacy of statin therapy for the primary prevention of cardiovascular (CV) disease has been demonstrated in several previous clinical trials. Statins have been shown to decrease the risk of CV events (CVE) and CV interventions (CVI). However, the residual risk of CVE or CVI in statin users has not been recently evaluated. Our objective was to determine the 5-year rates of the composite primary endpoint of CVE and CVI in patients who received statins for primary CV prevention. We also aim at identifying the independent predictors of the composite primary endpoint in this population.

Method: The CARTaGENE study was a cohort study of participants from Quebec, Canada (2009-2010). We included only participants who were using statins at the time of enrollment and excluded subjects with a self-reported history of cardiovascular disease (CVD) or a previous hospitalization for CVD within the last 5 years.
CVE included CV death, nonfatal myocardial infarction, unstable angina and non-hemorrhagic stroke. CVI was defined as either coronary, carotid or peripheral revascularization. The primary endpoint was the 5-year composite endpoint of CVE and CVI.
We identified independent predictors for the primary outcome by completing Cox proportional hazard models.

Results: Of the 18 833 participants with available low-density cholesterol (LDL-C) and no prior CV disease, 3 322 individuals (17.6%) were on statin therapy. The mean age was 58.9 years; 62.7% males, 48.3% hypertensives, 26.6% diabetics and 15.3% were active smokers. The 5-year rates of primary endpoint, CVE and CVI were 7.8%, 6.9% and 5.6% respectively.
We recorded 230 CVE events of which 83.5% were acute coronary syndrome, 10.9% were ischemic stroke/transient ischemic attacks and 5.6% were ischemic limb events.
The independent predictors for the primary endpoint were age (hazard ratio(HR) 1.06), male gender (HR 3.02), active smoking (HR 2.24), family history of myocardial infarction (HR 1.44), glomerular filtration rate less than 60 ml/min/1.73 m2 (HR 1.45), HB A1c, per % (HR 1.29), triglycerides, per mg/dl (HR 1.001) and uric acid, per mg/dl (HR 1.12).

Conclusion: The 5-year rates of CVE and CVI remained significant in statin users without prior CVD. Age, male sex, active smoking, family history of myocardial infarction, hypertriglyceridemia, hyperuricemia and increased glycosylated hemoglobin (HbA1C) were independent predictors of CVE or CVI in these patients. These results reinforce the need for a multi-faceted approach to further reduce CV risks in statin users for primary prevention.

Keywords: primary prevention, statin, coronary artery disease

An Evaluation of the Use of Propensity Scores in the Cardiovascular Literature: A Systematic Review and Recommendations

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Abstract has been withdrawn at the presenter's request. (

What's new in familial hypercholesterolemia in Canada? Results from the FHCanada registry.

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Familial hypercholesterolemia (FH) is the most frequent genetic lipoprotein disorder associated with premature CAD. The prevalence of FH in the general population has been recently revised to 1 in 250, so in Canada, the burden of disease is now estimated to be more than 143,000 patients, with less than 5% of patients diagnosed so far.

Objective: The goal of the FHCanada registry initiative was to create a registry of subjects with FH across Canada designed to identify subjects with FH and to improve health and healthcare delivery.

Methods: The registry regroups more than 200 basic researchers, clinicians and industry partners from across Canada (19 main academic centers and many peripheric sites). The database is using a uniform set of criteria and data entry, which includes clinical, biochemical and demographic information. Specimens (plasma/serum/DNA) are collected for local biobanking.

Results: More than 3,200 patients have been entered in the database so far. The FHCanada registry has a strong knowledge translation component (www.fhcanada.net). The registry network members worked together to implement evidence-based clinical practice guidelines for the diagnosis and treatment of FH, which were recently published in the Canadian Journal of Cardiology. The FH registry network has also worked on the creation of educational resources and web-based applications to simplify FH diagnosis and treatment. These include a new simplified clinical definition of FH for the Canadian population, a new algorithm for the imputation of baseline LDL-C from LDL-C on lipid-lowering therapy, and a new application to ease the clinical diagnosis of FH, the "FH calculator" (www.circl.ubc.ca). Most recently, the first CLIA-certified molecular diagnostic test for FH has been designed and validated and this genetic test is now available to all physicians across the province and in the rest of Canada.

Conclusion: Through the creation of a Canada-wide network, the FHCanada registry is implementing useful tools, which will significantly improve the diagnosis of FH and care to patients with FH and reduce cardiovascular disease in this population at high risk.

Keywords: familial hypercholesterolemia, diagnostic tools, genetic disorder

Design, development and early testing of a novel deployable Left Ventricular Assist Device.

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Background: Over the last decades, the use of continuous Left Ventricular Assist Devices (LVADS) as a treatment for patients with advanced heart failure has increased. Although these devices improve the quality of life and the survival rate, blood trauma adverse events such as infections, hemolysis, and thrombosis; remain to be an unmet challenge in the field of mechanical circulatory assist support. Studies suggest that these complications are due to the high shear stress levels, the high operating point, and the morphology of the device.
At the present time, the development of LVADs focuses on the evaluation of different configurations aiming to reduce the blood trauma to achieve long-term hemocompatibility.
The purpose of this study is to demonstrate the proof-of-concept of a novel low operating point axial-flow LVAD configuration through the experimental in-vitro assessment of the hydraulic performance curves. The design of this configuration relies on the way the blades are mounted on the housing of the pump, opening the possibility of a percutaneous deployable minimally invasive implantation mechanism.

Methods: Using CTturbo Software, Solidworks, and a Form2 3D stereolithography printer; two prototypes with correct anatomical dimensions were designed. The design operating point for the pump was 3 L/min, 100 mmHg and a rotational speed of 3200 RPM. An in-vitro test-rig was constructed. The test rig successfully measures and storage the pressure and flow across the pump and the power required to drive the pump at a sampling frequency of 500 Hz. Blood was modeled as a Newtonian fluid with a dynamic viscosity of 3.5 cP and a density of 1092 kg/m3 as the assumption of blood as a Newtonian fluid becomes acceptable at high shear rates (>100/s), such as the case of the LVADs.

Results: The performance curves for both prototypes were obtained at an operating speed of 3200 RPM. The first prototype produced a maximum flow of 1.7 L/min and 11 mmHg, whereas the second prototype included a secondary diffuser aiming to convert the kinetic energy into pressure and produced 2.2 L/min, and 15 mmHg.

Conclusion: The results demonstrate the feasibility of the novel LVAD configuration. The device provides physiological circulatory support at a low operating point. Improving the blade design and pump length dimensions would substantially increase the pressure to bring the performance curves closer to the design operating regime. The in-vitro test rig provides valuable device performance feedback for design optimization prior the hemolysis blood evaluation.

Keywords: left ventricular assist device, deployable, performance curve, in-vitro testing, test-rig

Incidence, Risk Factors and Mortality Associated with Infective Endocarditis in Pregnancy

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Background: Infective endocarditis (IE) is a rare infection in pregnancy. The purpose of this study was to evaluate the risks, outcomes, and predictors of death among pregnancies complicated with IE.

Methods: We carried out a cohort study on all births within the Health Care Cost and Utilization Project - Nationwide Inpatient Sample (HCUP- NIS) from 1999 - 2015. Among these women, demographic and baseline clinical risk factors were compared in individuals with and without IE and unconditional logistic regression was used to estimate the effect of risk factors on associated maternal mortality.

Results: There were 15,335,288 deliveries from 1999-2015 in the United States, among which 487 cases of IE were identified. As compared to women with no IE, women with IE in pregnancy tended to be older (35+), Caucasian, and reported income within the lowest quartile. Women with IE were more commonly found to have a history of prior valvular disease, congestive heart failure (CHF), rheumatic heart disease and drug abuse as compared to women with no IE. Staphylococcus species was the most commonly implicated organism, accounting for 70.8% of total cases. In women with IE in pregnancy, 11.5% underwent valve replacement surgery. Mortality with IE was 5% ($p<.0001$). In adjusted analyses, CHF (OR 3.33, $p<.01$), acute myocardial infarction (MI) (OR 31.8, $p<.001$) and sepsis (OR 12.7, $p<.001$) were all associated with a significantly increased risk of death.

Conclusion: IE is rare but associated with an increased risk of maternal morbidity and mortality. Pregnancies with suspected IE should be transferred to centers capable of providing cardiac surgery and intensive care.

Keywords: pregnancy, infective endocarditis, outcomes pregnancy, microbiology

P2X7 receptor plays a role in angiotensin II-induced hypertension and vascular remodeling

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Introduction: Inflammasome activation by binding of ATP released from damaged cells to the purinergic receptor P2X7 (P2RX7) could play a role in hypertension and vascular injury through release of interleukin (IL)-1β and immune cell activation. Elevated ATP levels were observed in the renal interstitial fluid of angiotensin (Ang) II-infused rats, and treatment of these rats with a non-selective P2 receptor blocker prevented Ang II-induced inflammation and renal damage. P2RX7 knockout (P2rx7–/–) prevented deoxycorticosterone acetate-salt-induced blood pressure (BP) elevation and renal damage. However, it is unknown whether the P2RX7 plays a role in Ang II-induced BP elevation and vascular damage. We hypothesize that Ang II-induced hypertension, vascular injury, and inflammation will be blunted in P2rx7-/- mice.

Methods: Ten to 12-week-old male C57BL/6J male wild-type (WT) and P2rx7–/– mice were sham-treated or infused with Ang II (490ng/kg/min) for 14 days. BP was determined by telemetry. Mesenteric artery function and remodeling was assessed using pressurized myography. P2RX7 expression in spleen immune cells was determined by flow cytometry. IL-1β secretion from bone marrow-derived macrophages (BMDM) isolated from WT and P2rx7–/– mice was assessed by ELISA.

Results: Stimulation with lipopolysaccharides and ATP caused IL-1β release in WT (339±162 pg/mL) but not P2rx7–/– BMDMs. In WT mice, Ang II increased P2RX7 expression in dendritic cells (mean fluorescence intensity: 1927±120 vs 3983± 983) and macrophages (2541±265 vs 3314 ±273 respectively). P2rx7 knockout reduced Ang II-induced systolic (159±3 vs 180±5 mm Hg) and diastolic BP elevation (114±5 vs 140 ±6 mm Hg) compared to WT mice. Acetylcholine-induced relaxation was unaffected by Ang II or P2rx7 knockout. Ang II increased the media-to-lumen ratio more in WT (5.02 ±0.54% vs 3.89 ±0.21%) than in P2rx7–/– mice (3.85±0.20% vs 3.31±0.25%).

Conclusion: This study demonstrated that P2RX7 plays a role in Ang II-induced hypertension and vascular remodeling.

Keywords: hypertension, immune, inflammation, P2X7, innate immunity

The Essential Frailty Toolset in Older Adults Undergoing CABG

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BACKGROUND: Frailty is prevalent and associated with adverse outcomes in older adults undergoing cardiac procedures; however, there remains uncertainty about the ideal tool to measure it. The Essential Frailty Toolset (EFT) was previously developed in patients undergoing aortic valve replacement procedures and found to be superior to other tools. The EFT has yet to be evaluated in patients undergoing coronary artery bypass grafting (CABG) surgery.

METHODS: Data was collected from a prospective cohort of patients ≥60 years of age undergoing CABG without concomitant valve replacement between 2011-2018 at two university hospitals (Jewish General Hospital, Royal Victoria Hospital; Montreal, QC). The EFT was assessed pre-operatively and scored 0 to 5 points as a function of five chair rises (1 point if >15 seconds, 2 points if unable), mini-mental status examination (1 point if <24), serum albumin (1 point if <35), and hemoglobin (1 point if <130 in men or <120 in women). The primary outcome was 1-year all-cause death or worsening disability defined as institutionalization or ≥2 new disabilities in basic or instrumental activities of daily living.

RESULTS: The cohort consisted of 520 patients with a mean age of 71.4 ± 6.4 years . The mean EFT score was 1.3 ± 1.1 points, with 137 (26%) being non-frail with an EFT of 0 points, 306 (59%) being pre-frail with an EFT of 1-2 points, and 77 (15%) being frail with an EFT of 3-5 points. The incidence of 1-year death or worsening disability was 6% in non-frail patients, 12% in pre-frail patients, and 29% in frail patients. After adjusting for the STS predicted risk of mortality in a Cox proportional hazards model, each incremental EFT point was associated with a hazard ratio of 1.41 (95% CI 1.10 to 1.82) for the primary outcome. After adjusting for individual covariates (age, sex, ejection fraction, redo, urgent surgery), each incremental EFT point was similarly associated with a hazard ratio of 1.44 (95% CI 1.14 to 1.83) such that frail patients had a 2.6 fold increase in the primary outcome.

CONCLUSION: The EFT is a valid, rapid, and highly prognostic tool to assess frailty in older adults undergoing CABG. Furthermore, the subdomains of the EFT may be actionable through targeted interventions such as cardiac rehabilitation, nutritional optimization, and iron replacement.

Keywords: frailty, CABG, outcomes, disability, survival

Sex Differences in the Efficacy of Renin Angiotensin Aldosterone System Blockers in Heart Failure with Reduced Ejection Fraction

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Background: Heart Failure with reduced ejection fraction (HFrEF) is a clinical syndrome with a large global burden and continues to have a high mortality rate despite advances in treatment. Renin angiotensin aldosterone system (RAS) blockers are the cornerstone of treatment. However, biochemical and epidemiological evidence suggests that the efficacy of RAS blockers may differ between men and women with HFrEF.

Methods: We conducted a retrospective exploratory post-hoc analysis of pooled data from the Study of Left Ventricular Dysfunction (SOLVD) and Candesartan in Heart Failure: Assessment of Morbidity and Mortality (CHARM) Alternative trials, to explore sex differences in the efficacy of RAS blockers in HFrEF. The primary outcome was a composite of death and hospitalization for heart failure (HHF). Patients were stratified by sex and treatment group, to obtain sex specific hazard ratios (HRs). Multivariate analyses were conducted using Cox proportional hazards models, adjusting for comorbidities and including a sex-by-drug interaction.

Results: Our analysis included 4597 participants (25% women; mean age 62.8±10.5 years). In both placebo and treatment groups, baseline clinical characteristics were similar regardless of sex. Over a period of 53 months, 1169 participants (51%) in the placebo group experienced the primary outcome, compared to 985 (43%) in the treatment group [hazards ratio, (HR) 0.76 95% Confidence Interval (CI) 0.70-0.83]. The effect of the treatment persisted after adjusting for multiple confounders [aHR, 0.72 95% CI 0.66-0.79]. However, the HR for primary outcomes was significantly lower only in men treated with RAS blockers but not in women [aHR-men 0.73 95% CI 0.66-0.80; aHR-women 0.85 95% CI 0.70-1.03, P-interaction=0.05)

Conclusions: The RAS blockers are associated with a lower risk of death and hospitalization than placebo, with a greater benefit in men than in women. Further research is needed to explain the reasons behind the reduced efficacy in women with HFrEF.

Keywords: heart failure, women, renin angiotensin aldosterone system

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