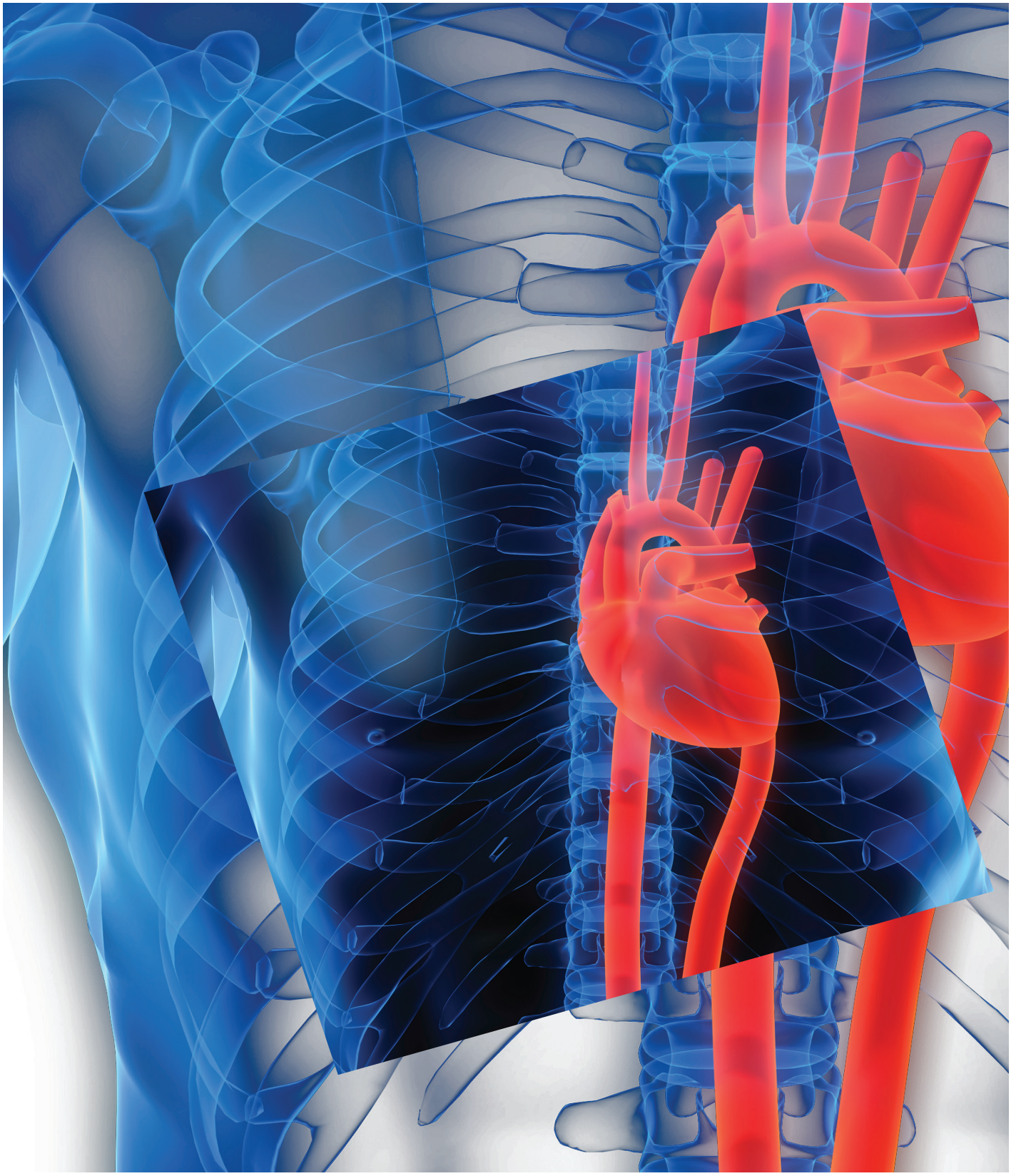
Maurice McGregor
CARDIOVASCULAR
RESEARCH DAY

Friday, May 27, 2022
8:30 a.m. - 2:30 p.m.



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Dr. Negareh Mousavi
Dr. Nicolo Piazza

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

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McGill University Heath Centre – Research Institute
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Program

Friday, May 27, 2022

8:30 - 8:40	Introduction	Michael Goldfarb, MD MSc
8:40 - 8:45	Opening Remarks	**Ernesto L. Schiffrin, C.M., MD, PhD, FRSC, FRCPC, FACP, FAHA** Physician-in-Chief, Department of Medicine, Jewish General Hospital Director, Hypertension and Vascular Research Unit, Lady Davis Institute for Medical Research Distinguished James McGill Professor and Vice-Chair (Research), Department of Medicine, McGill University
8:45 - 10:15	Oral Presentations Session #1 Moderator: Thao Huynh Thanh, MD PhD	8:45 Fayeza Ahmad: De-Frailing Cardiac Inpatients with a Multicomponent Intervention in the TARGET-EFT Randomized Clinical Trial 9:00 Kevin Comeau: Memory Gamma Delta T Cells Play a Role in Hypertension 9:15 Khalil Anchouche: Long-term effects of Lipoprotein(a) on Aortic Valve Calcium incidence and progression in the Multi-Ethnic Study of Atherosclerosis 9:30 Francisco Rios: Spike protein 1 of SARS-CoV-2 increases endothelial cell dysfunction via Interferon activation pathways 9:45 Hristo Valtchanov: In-Silico Assessment of the Affect of Hemolysis on Thrombosis in Ventricular Assist Devices 10:00 Zahra Sohani: Sex differences in the effectiveness of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and sacubitril-valsartan in heart failure
10:15 - 10:30	Break	

10:30 - 12:00	Oral Presentations Session #2 Moderator: Abhinav Sharma, MD PhD	10:30 Brandon Shokoples: P2RX7 antagonism blunts angiotensin II-induced hypertension, vascular injury and CD8+ T cell activation without the cardiac dysfunction induced by P2rx7 knockout 10:45 Leila Haririsanati: Accuracy of Native Myocardial T1 and T2 mapping for Quantifying Ischemic Myocardial Injury 11:00 Ida Derish: Interpatient Differences in Induced Pluripotent Stem Cell-Derived Cardiomyocytes After Hypoxia 11:15 Justin Miron: Effect of serum lipoprotein(a) levels on the progression to atherosclerotic cardiovascular disease in carriers of familial hypercholesterolemia variants 11:30 Shiwon Choi: Docetaxel is an anti-dyslipidemic and anti-atherogenic drug candidate 11:45 Mohammad Sazzad Hasan: Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Hematopoietic Cancer in Children with Congenital Heart Disease
12:00 - 1:00	**2020 Louis & Artur Lucian Award Lecture**	**David Kass, MD** Abraham and Virginia Weiss Professor of Cardiology Professor of Medicine Departments of Medicine, Biomedical Engineering, Pharmacology and Molecular Sciences, and Cellular and Molecular Medicine and Pathobiology Johns Hopkins Medicine **PDE9 Inhibition to Treat Heart Failure and Obesity**
1:00 - 2:00	Poster Presentations Session #3	Virtual poster presentations: Finalists

	Moderator: Guenievre Grondin	1:00 Rosie Fountotos: Multicomponent Geriatric Intervention for Frail Hospitalized Older Adults with Cardiovascular Disease: The TARGET-EFT Randomized Clinical Trial 1:10 Johnathan Grossman: Pulmonary valve replacement in Tetralogy of Fallot: Risk of redo and comparison to the Ross procedure in a pan-Canadian study 1:20 Justine Desrochers: Risk Factors Modify the Strength of a Coronary Artery Disease Genetic Risk Score 1:30 Anouar Hafiane: Apolipoprotein A-I carboxy-terminal domain residues 187-243 are required for adiponectin-induced cholesterol efflux 1:40 Amanda Guerin: Genetic Testing for Familial Hypercholesterolemia in the Province of Québec: Update on a Retrospective Cohort Study 1:50 Kate Lindsay: Sex and body composition differentially impact the myocardial oxygenation response to breathing maneuvers
2:00 - 2:15	Awards:	
2:15 - 2:30	Closing remarks	**Ariane Marelli MD, MPH, FRCPC, FACC, FAHA** Professor of Medicine, McGill University Founder, McGill Adult Unit for Congenital Heart Disease Director of Research and Academic Affairs Cardiology, McGill University Health Center

Keynote Speaker

David A. Kass, M.D.
Abraham and Virginia Weiss Professor of Cardiology
Professor of Medicine
Professor of Pharmacology and Molecular Sciences
Professor of Biomedical Engineering
Director, Institute of CardioScience
Johns Hopkins University School of Medicine

David Kass received his BA from Harvard College where he majored in Applied Physics and Engineering, and in MD from Yale University. He completed his residency in Internal Medicine at George Washington University, in Washington DC, and in the early 1980's joined the Division of Cardiology at Johns Hopkins University first as a fellow and subsequently as a faculty member, where he has remained ever since. Among his many honors are the 2020 Louis and Artur Lucian Award, the American Heart Association Basic Science Award, George Brown Lectureship, and Inaugural Melvin Marcus Award, Peter Harris Distinguished Scholar Award and Innovator Award from the International Society of Heart

Research, and National Institutes of Health Outstanding Investigator Award. His research is expansive, providing innovative landmark studies in many different fields of cardiovascular science, spanning from basic molecular and cellular studies through to human clinical trials. He lists nearly 500 original papers, many book chapters and reviews, garnering >71,000 citations with an H-index of 141. He is considered a world leader in the pathobiology and therapy of heart failure, cardiac physiology and mechanics, and cyclic GMP-protein kinase G and phosphodiesterase signaling. He pioneered the clinical development of cardiac resynchronization therapy first in patients and later in basic mechanistic studies. Over the past 20 years, his lab has reported landmark studies regarding cGMP/protein kinase G signaling revealing new methods to stimulate this pathway to treat heart disease and identifying novel downstream effectors. This has resulted in active research in the treatment of Duchenne muscular dystrophy, heart failure and hypertrophy, obesity, and adoptive immuno-cell therapy for cancer. Dr. Kass has directly mentored over 100 students in his laboratory, most now active in academics and many with leadership roles in cardiovascular research.

Abstracts for Oral Presentations

De-Frailing Cardiac Inpatients with a Multicomponent Intervention in the TARGET-EFT Randomized Clinical Trial

Fayeza Ahmad[1, 2], Rosie Fountotos[1, 2], Neetika Bharaj[2, 3], Haroon Munir[1, 2], Kiana Hagerty[4], Mojdeh Moussavi Hedzazi[4], John Marsala[4], Lawrence Rudski[4], Michael Goldfarb[1, 4], Jonathan Afilalo[1, 2, 4]

[1]Division of Experimental Medicine, McGill University, Montreal, Canada, [2]Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Canada, [3]Department of Kinesiology & Physical Education, McGill University, Montreal, Canada, [4]Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Canada

Background: Frailty, a geriatric syndrome defined by an increased vulnerability to stressors and functional decline, is disproportionately prevalent in cardiovascular disease patients. Previous studies show that physical frailty assessed at the time of hospital discharge is associated with subsequent functional decline and mortality. We hypothesized that a multicomponent geriatric intervention would improve physical frailty in vulnerable older adults admitted with cardiovascular conditions.

Methods: We used data from TARGET-EFT, a randomized clinical trial that enrolled patients ≥65 years of age with pre-frailty or frailty (Essential Frailty Toolset score ≥1) admitted to the cardiovascular ward at the Jewish General Hospital, an academic tertiary care center in Montreal, Canada. Based on identified frailty deficits, the intervention group received bi-daily visits for 20 minutes consisting of individualized exercises focusing on mobility, resistance training and flexibility, bi-daily cognitive stimulation activities, nutritional supplementation and iron replenishment, if deficient. The control group received usual clinical care. Physical frailty was measured by the Short Physical Performance Battery (SPPB) at discharge and a sarcopenia questionnaire (SARC-F) ascertained by a blinded observer at 30 days post-discharge. Linear regression was used to determine the effect of our intervention on these continuous scores after adjusting for baseline scores and duration of the intervention.

Results: Out of 150 patients randomized in the intention-to-treat analysis, 135 survived and completed the SPPB at discharge, all but two of which also completed the SARC-F at 30 days post-discharge. The mean age was 79.3 ± 7.7 years with 54% females. Two major reasons for admission were heart failure (28%) and ischemic heart disease (28%). The mean duration of the in-hospital intervention was 11.0 ± 11.7 days. The mean SPPB and SARC-F scores at baseline were 4.5 ± 3 and 5.2 ± 2.6, respectively. Compared to usual care, the intervention led to a +1.52-point superior SPPB score (95% CI 0.75, 2.28; P<0.001; effect size 0.5) and a -0.74-point superior SARC-F score (95% CI -1.38, -0.11; P=0.02; effect size 0.3).

Conclusions: Our multicomponent intervention targeted to the deficits of older cardiac inpatients led to clinically meaningful improvements in short-term physical frailty, which has been associated with improved functioning and reduced morbidity post-hospitalization.

Gamma Delta T Cells Play a Role in Hypertension

Kevin Comeau[1], Pierre Paradis[1], Ernesto Schiffrin[2]

[1]Hypertension and Vascular Research Unit, Lady Davis Institute for Medical Research, [2]Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, Quebec, Canada

Background: A subset of T cells, γδ T cells, participate in the pathogenesis of hypertension. It was shown that memory T cells develop after an initial hypertensive insult, sensitizing mice to develop hypertension to subsequent mild hypertensive stimuli. However, whether memory γδ T cells develop and play a role in hypertension remains unknown. We hypothesize that memory γδ T cells form after exposure to a hypertensive stimulus, and that they sensitize mice to mild hypertensive insult.

Methods: Ten-12-week-old C57BL/6J mice were infused or not with a pressor dose of angiotensin II (AngII) (490 ng/kg/min, SC) for two weeks, followed by a two-week washout period, and then infused with a subpressor dose of AngII (140 ng/kg/min, SC) for two weeks. Blood pressure (BP) was measured by telemetry and memory γδ T cells profiled by flow cytometry. Another group of mice was treated as above, but injected IP with 400 mg of anti-T cell receptor γδ-depleting or isotype control antibodies 1 day before and 6 days after the initiation of the second hypertensive challenge. A final group of mice was injected IV with $2.5x10^5$ live γδ T cells isolated from spleens and lymph nodes of mice exposed or not to a hypertensive challenge, and then mice were exposed to a subpressor AngII infusion as above.

Results: Mice exposed to repeated hypertensive challenges had a 27 mm Hg higher systolic BP than mice exposed to only the mild hypertensive challenge ($P<0.001$). Fourteen days of pressor AngII infusion increased effector memory γδ T cells 5.2-fold in the mesenteric artery perivascular adipose tissue (PVAT) and 1.8-fold in the mesenteric lymph nodes (mLNs) compared to sham ($P<0.05$). Repeated AngII infusion decreased central memory γδ T cells by 57% in aortic PVAT and by 22% in mLNs compared to controls ($P<0.05$). Mice depleted of γδ T cells had a 9% lower systolic BP than control mice over the final week of the second hypertensive challenge ($P<0.05$). Preliminary results indicate that adoptive transfer of γδ T cells from hypertensive into normotensive mice increased BP elevation to low dose AngII infusion.

Conclusion: Initial exposure to a hypertensive stimulus causes development of memory γδ T cells and sensitizes mice to develop hypertension to a subsequent subpressor hypertensive challenge. Depleting γδ T cells reduces the BP response to a second, mild hypertensive challenge. Transfer of hypertensive γδ T cells may sensitize mice to develop hypertension to a mild hypertensive stimulus.

Long-term effects of Lipoprotein(a) on Aortic Valve Calcium incidence and progression in the Multi-Ethnic Study of Atherosclerosis

Khalil Anchouche[1], Line Dufresne[1], James Engert[1], George Thanassoulis[1]

[1]MUHC

Background: Aortic stenosis (AS) is widely prevalent, with over 2.5 million patients affected in North America. Genome-wide association studies have previously demonstrated an association between lipoprotein(a) (Lp[a]) and AS, findings which have since been corroborated by numerous Mendelian randomization studies. To date, however, there has been limited prospective data examining the association between Lp(a) and aortic valve calcium (AVC) over extended follow-up.

Methods: We included in our analysis all participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) for whom baseline (Exam 1) and 10-year (Exam 5) CT data was available. We used AVC, reported in Agatston units, as a surrogate for the presence of calcific AS. In participants with AVC=0 at baseline, we used an ordered logistic regression to estimate the odds ratio of log-Lp(a) on AVC severity (=0, 0-100, and ≥100) at Exam 5. In participants with AVC>0 at baseline, we used a generalized linear model (GLM) with gamma distribution to estimate the effect size of log-Lp(a) on the increase in AVC from baseline. To account for correlation between serial measurements, we used a generalized estimate equation (GEE) to determine the effect of log-Lp(a) on AVC over time.

Results: Of the 6,814 participants in MESA, 3,057 were included in our analysis; 2,015 (65.9%) of these had Lp(a) data. Within this cohort, 2,740 (89.6%) participants had AVC = 0 at baseline, while only 317 (10.4%) had AVC > 0. The mean age was 60 ± 9.4 years, 48.3% were male and 40.8%, 10.0%, and 48.7% reported a history of hypertension, diabetes, and smoking, respectively. In individuals with AVC=0 at Exam 1, the odds of developing AVC at Exam 5 increased by OR=1.22 ([1.07 – 1.53], p=0.0245) per standard-deviation (SD) of log-Lp(a). However, in individuals with AVC>0 at Exam 1, Lp(a) was not associated with AVC progression (β = 1.1 [0.82 – 1.47], p=0.50). In the longitudinal analysis, log-Lp(a) did not have a significant association with AVC, (β = 4.75 [-0.47 – 9.96], p=0.074). When including time in the GEE model, we found no significant change in AVC with log-Lp(a) (β = 1.53 [-0.29 – 3.34], p=0.099).

Conclusion: In the MESA cohort, Lp(a) was associated with the incidence of AVC in participants without baseline aortic valve calcific disease over 10-year follow-up. Further analyses will be required to assess the effect of Lp(a) on progression of AVC in patients with pre-existing calcific aortic valve disease.

Spike protein 1 of SARS-CoV-2 increases endothelial cell dysfunction via Interferon activation pathways

Francisco J Rios[1], Augusto C Montezano[1], Livia L Camargo[1], Rheure Alves-Lopes[1], Ana B Garcia-Redondo[2], Eliju Aranday-Cortes[3], Ana M Briones[2], John McLauchlan[3], Rhian M Touyz[4]

[1]BHF-ICAMS - University of Glasgow, Glasgow, UK, [2]Departamento de Farmacología, Universidad Autónoma de Madrid. Instituto de Investigación Hospital La Paz, Madrid, Spain., [3]MRC-Centre for Virus Research - University of Glasgow, Glasgow, UK, [4]Research Institute of the McGill University Health Centre

Background: COVID19-associated immunopathology is associated with increased production of interferon (IFN)-alpha (IFNα) and lambda3 (IFNL3). Effects of IFNs are mediated by interferon-stimulated genes (ISGs) and influence expression of angiotensin-converting enzyme 2 (ACE2), the receptor for S-protein (S1P) of SARS-CoV-2. Increasing evidence indicates vascular inflammation in cardiovascular sequelae of COVID19. We hypothesized that S1P-induced immune/inflammatory responses in endothelial cells (EC) are mediated via IFNs.

Method: Human ECs were stimulated with S1P (1μg/mL), IFNα (100ng/mL) or IFNL3 (100IU/mL). Because ACE2, metalloproteinase domain-17 (ADAM17) and type-II transmembrane serine protease (TMPRSS2) are important for SARS-CoV-2 infection, we used inhibitors of ADAM17 (marimastat, 3.8nM), ACE2 (MLN4760, 440pM), and TMPRSS2 (camostat, 50μM). Gene and protein expression was investigated by real-time PCR immunoblotting, respectively. Vascular function was assessed in mesenteric arteries from wild-type (WT) normotensive and hypertensive mice and in ISG15-deficient (ISG15KO) mice.

Results: EC stimulated with S1P increased expression of IFNα (3-fold), IFNL3 (4-fold) and ISG (2-fold)($p<0.05$). EC exhibited higher responses to IFNα (ISG15: 16-fold) than to IFNL3 (ISG15: 1.7-fold)($p<0.05$). S1P increased gene expression of IL-6 (1.3-fold), TNFα (6.2-fold) and IL-1β (3.3-fold), effects that were maximized by IFNs. Only marimastat inhibited S1P effects. IL-6 was increased by IFNα (1,230pg/mL) and IFNL3 (1,124pg/mL) vs control (591pg/mL). This was associated with increased phosphorylation of Stat1 (134%), Stat2 (102%), ERK1/2 (42%). Nitric oxide production and eNOS phosphorylation (Ser1177) were reduced by IFNα and (40%) and IFNL3 (40%). Reduced endothelium relaxation maximal response (%Emax) was observed in vessels from WT-mice stimulated with IFNα (67%) and IFNL3 (71%) vs control (82%) ($p<0.05$) but not in vessels from ISG15KO mice. Increased contraction was observed only in vessels from hypertensive mice treated with IFNα (9.1±0.5mN vs control: 7.3±0.3mN, $p<0.05$).

Conclusion: In ECs, S1P, IFNα and IFNL3 increased ISG15 and IL-6, processes that involve ADAM17. Inflammation induced by S1P was amplified by IFNs. IFNs induce vascular dysfunction through ISG15-dependent mechanisms, with augmented effects in hypertension. Our findings demonstrate that S1P induces immune/inflammatory responses that may be important in endotheliitis associated with COVID-19. This is especially important in the presence of cardiovascular risk factors, including hypertension.

In-Silico Assessment of the Affect of Hemolysis on Thrombosis in Ventricular Assist Devices

Hristo Valtchanov[1], Rosaire Mongrain[1], Renzo Cecere[2]

[1]Department of Mechanical Engineering, McGill University, [2] Department of Surgery, Faculty of Medicine and Health Sciences, McGill University

Background: Non-physiological flow conditions present within ventricular assist devices (VADs) impose high mechanical stresses on blood constituents that cause blood damage in the form of hemolysis and thrombosis. Lethal hemolysis and occluding thrombus occur rarely in modern VADs, however, the incidence of thromboembolic complications remains persistently high. Plasma free hemoglobin (pfHb) is known to induce hypercoagulability by binding to both fibrin and von-Willebrand Factor, increasing the rate of platelet adhesion by up to a factor of six. Furthermore, ADP released from hemolyzed red blood cells is a potent platelet activator, potentially circumventing anti-coagulation medications that target platelet activation such as heparin. Consequently, it is important to untangle which of these effects most severely affects thrombosis, and secondly to gauge the magnitude of these effects on the likelihood of thrombus growth.

Method: An In-silico approach is used wherein fluid flow and stresses are simulated computationally in a VAD, shown in Figure 1. Hemolysis and the chemical kinetics of the intrinsic coagulation pathway are simulated computationally by solving advection-diffusion-reaction equations that govern activation and adhesion of platelets to the VAD surfaces. The effect of hemolysis on thrombosis is directly incorporated into the model by assuming that ADP is released from hemolyzed red blood cells in direct proportion to pfHb concentration, and that platelet adhesion rates vary spatially with the concentration of pfHb. Parameters varied were limited to rotor speed, the concentration of heparin, whether hemoglobin concentration affected platelet adhesion rates, and whether ADP was released during hemolysis. Nominal values were used and held constant for all other parameters such as blood temperature, inflow rate, platelet counts, hemocrit, and VAD material.

Results: In the absence of anticoagulation, it was found that small circular blood clots formed on the surface of the VAD in regions of low wall shear-stress and high concentrations of activated platelets. Blood clots situated in regions of higher shear stress, such as on the rotor, stabilized in size over time, whereas others grew indefinitely. Increasing the level of anticoagulation reduced the number of these clots. The number and size of blood clots increased drastically when pfHb was allowed to increase platelet adhesion, even at subclinical hemolytic levels. ADP released during hemolysis had a similar affect but required higher hemolytic levels.

Conclusion: It was found that subclinical hemolytic activity led to the formation of small blood clots, even in the presence of high levels of anticoagulation by Heparin.

Sex differences in the effectiveness of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and sacubitril-valsartan in heart failure

Zahra Sohani[1]

[1]McGill University Health Centre

Background: Practice guidelines for congestive heart failure (CHF) are largely based on trials conducted predominantly in men with reduced ejection fraction. However, recently PARAGON-HF suggested a potential benefit of *sacubitril-valsartan* among women with preserved ejection fraction. To this end, among patients with CHF previously treated with ACE inhibitors or ARBs, we assessed effectiveness of treatment with *sacubitril-valsartan* compared to ACEI/ARB monotherapy and studied whether this effect differed between men and women for both preserved and reduced ejection fraction.

Methods: Data was derived from the Truven Health MarketScan Databases between January 1, 2011 and December 31, 2018. We included patients with a primary diagnosis of CHF on treatment with ACE inhibitors, ARBs, or *sacubitril-valsartan* based on the first prescription after diagnosis. Patients were followed until an outcome occurred or were lost to follow-up. 7,181 patients treated with *sacubitril-valsartan*, 25,408 patients using an ACEI, and 16,177 patients treated with ARBs were included. The studied outcomes were a composite of readmissions for HF and death from cardiovascular causes and composite of readmissions, death, myocardial infarction, stroke, and cardiac arrest. We secondarily assessed safety outcomes.

Results: A total of 790 readmissions or deaths occurred among 7,181 patients in the *sacubitril–valsartan* group and 11,901 events in 41,585 patients treated with ACEI/ARB. Adjusted for covariates, the hazard ratio (HR) for treatment with *sacubitril–valsartan*compared to ACEI or ARB was 0.74, 95% CI 0.68-0.80. The protective effect of sacubitril–valsartan was evident for men and women (HR women 0.77, 95% CI 0.68–0.88; HR men 0.73, 95% CI 0.66–0.82). The effect for both sexes was seen mostly in systolic dysfunction.

Conclusions: Treatment with *sacubitril–valsartan* is more effective at reducing mortality and admission to hospital for heart failure compared to ACEI / ARBs equally among men and women with systolic dysfunction; sex differences in the effectiveness of *sacubitril-valsartan* in diastolic dysfunction requires further investigation.

P2RX7 antagonism blunts angiotensin II-induced hypertension, vascular injury and CD8+ T cell activation without the cardiac dysfunction induced by P2rx7 knockout

Brandon Shokoples[1, 2], Kevin Comeau[1, 2], Pierre Paradis[1], Ernesto Schiffrin[1, 2, 3]

[1]Lady Davis Institute for Medical Research, [2]McGill University, [3]Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital

Background: The P2X7 receptor (P2RX7) recognizes damage associated molecule patterns such as extracellular adenosine triphosphate (ATP) and triggers the activation of immune cells. Elevated plasma ATP levels have been observed in hypertensive patients, providing a potential mechanism for P2RX7 activation. Additionally, a hypomorphic polymorphism for *P2RX7* is correlated with a decreased risk for essential hypertension in Chinese post-menopausal women. However, it is unknown whether P2RX7 activation contributes to angiotensin (Ang) II-induced blood pressure (BP) elevation and cardiovascular damage. We hypothesized that *P2rx7* knockout or P2RX7 antagonism would blunt Ang II-induced BP elevation, and cardiovascular injury through decreased immune activation.

Methods: Ten-to-12-week-old male C57BL/6J wild-type (WT) and *P2rx7*$^{-/-}$ mice were infused or not with Ang II (1000 ng/kg/min) for 14 days. A second group of WT mice infused with Ang II was infused with the P2RX7 antagonist AZ10606120 (694 ng/kg/min) or vehicle for 14 days. BP was determined by telemetry, mesenteric artery function using pressurized myography, cardiac left ventricle function by ultrasound and infiltration of activated immune T cells in aortic perivascular adipose tissue (PVAT) by flow cytometry.

Results: Ang II-induced systolic BP elevation was reduced by *P2rx7* deficiency (*P2rx7*$^{-/-}$ vs WT: 164±3 vs 176±2 mm Hg, $P<0.05$) or P2RX7 antagonism (AZ10606120 vs vehicle: 143±5 vs 170±5 mm Hg, $P<0.01$). Ang II-treatment impaired left ventricle fractional shortening (FS) in WT mice (43.8±2.4% vs 32.5±3.1%, $P<0.05$), which was exacerbated in *P2rx7*$^{-/-}$ mice (20.2±3.1%, $P<0.05$ vs WT Ang II), but not in mice receiving AZ10606120 (28.9±3.3%). Ang II-induced mesenteric artery endothelial dysfunction in WT mice (61±7 vs 83±4% relaxation response to acetylcholine, $P<0.05$), was absent in *P2rx7*$^{-/-}$ (89±3%) or AZ10606120-treated mice (86±3%). Ang II caused a 3.8-fold increased infiltration of activated $CD8^+$ T cells in aortic PVAT of WT mice (60±16 vs 16±3 cells/aortic PVAT, $P<0.001$), which was absent in *P2rx7*$^{-/-}$ mice (27±7 cells/aortic PVAT) or AZ10606120-treated mice (8±2 cells/aortic PVAT).

Conclusion: *P2rx7* knockout or antagonism attenuates Ang II-induced hypertension, vascular injury, and infiltration of activated $CD8^+$ T cells into aortic PVAT. *P2rx7* knockout exacerbated cardiac dysfunction, whereas P2RX7 antagonism did not.

Accuracy of Native Myocardial T1 and T2 mapping for Quantifying Ischemic Myocardial Injury

Leila Haririsanati[1], Katerina Eyre[1], Elizabeth Hillier[1], Ria Garg[2], Michael Chetrit[1], Matthias G. Friedrich[1]

[1]McGill, [2]Geisinger Commonwealth

Background: Late gadolinium enhancement (LGE) cardiac magnetic resonance imaging is the clinical gold standard method to evaluate fibrosis in ischemic cardiomyopathy (ICMP) patients. LGE is time-consuming, costly and may result in possible side effects. Native (contrast-free) T1/T2 mapping have the potential to assess myocardial injury faster and more safely. This study evaluated the agreement between the presence and extent of myocardial injury measured with T1/T2 mapping and LGE in an ICMP patient population.

Methods: We retrospectively studied patients with suspected ICMP who had undergone a clinical exam including LGE and T1/T2 maps. Irreversible injury was defined in LGE images as an area with increased signal intensity (> 5 standard deviations (SD) above reference tissue). In the T1/T2 maps, this pathologic area was defined as an increase of ≥ 2SD above our local reference values. The presence and extent of positive LGE/elevated T1 areas were compared between paired short-axis T1 maps and LGE images. The presence of elevated T2 times in the area with positive LGE and elevated T1 times was assessed to identify the acute myocardial injury.

Results: We enrolled 32 patients (mean age: 64.06±13.06 years old, 9% females). There was a moderate to strong agreement between T1 maps and LGE (Apex 0.66, mid-ventricle 0.93, basal 0.87) in identifying the presence of myocardial injury. The agreement between T2 maps and LGE in all slices was moderate to strong (Apex 0.68, mid-ventricular 0.82, basal 0.65). The extent of the myocardial injury area in chronic cases was not significantly different between LGE and T1 maps (p=0.31). In acute cases which included 57% of total slices, T1 maps identified a significantly larger area of myocardial injury than LGE (p<0.001). However, T2 maps and LGE had a similar extent of myocardial injury (p values apex= 0.45, mid-ventricle= 0.18, basal= 0.18) in acute cases.

Conclusions: In patients with ischemic myocardial injury, there is a moderate to strong agreement between T1/ T2 maps and LGE in identifying the injured area. In chronic cases, the extent of the injured area using T1 maps is similar to that in LGE images, while the same is the case for T2 maps in acute injury. This finding suggests that non-contrast images may, at least in addition to other images, be used to identify myocardial injury. While T1 allows for estimating the size of chronic injury, T2 does so for acute infarcts. Future studies in larger samples should be performed to investigate the utility of combining image information.

Interpatient Differences in Induced Pluripotent Stem Cell-Derived Cardiomyocytes After Hypoxia

Ida Derish[1], Bin Yu[2], Jeremy Zwaig[1], David Derish[3], Janice To[4], Patrick Young[5], Renzo Cecere[6]

[1]Department of Experimental Surgery, [2]Department of Experimental Medicine, [3]Department of Medicine, [4]Department of Pharmacology, [5]Department of Kinesiology, [6]Department of Cardiac Surgery

Background: The increasing rate of cardiovascular disease (CVD) in surviving patients contributes to a worsening quality of life as well as a socioeconomic burden on the healthcare system. Newly approved therapies present unforeseen side effects and occasionally entail adverse cardiovascular responses in patients. Indeed, modern treatments do not account for the variability of individual patient reactions, due to a lack of a representative *in vitro* cardiac model. While the use of induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) has gained traction as a viable model when compared to cardiac biopsies and immortalized cell lines, cardiovascular patient-specific differences remain poorly understood and understudied. We hypothesized that 1) cardiomyopathic patient-derived iPSC-CMs have differing baselines of beating rate, contractility, viability and metabolic activity, when compared to healthy controls, and that 2) cell lines have patient-specific responses to hypoxic injury. The purpose of this study was to perform a characterization of patient-derived iPSC-CM function, and to study patient-specific cellular responses to hypoxia.

Methods: First, we generated iPSCs (n=5 cardiomyopathic patients, n=2 healthy donors). from peripheral blood through transfection of reprogramming factors (Oct4, Sox2, Lin28, Klf4, and L-Myc) and performed an assessment of cell line quality via immunocytochemistry (OCT4, Nanog, SSEA-4 and TRA-1-60), RT-PCR (SOX2, Lin28, NANOG, TDG1, Oct3/4, DPPB5) as well as trilineage differentiation immunostaining (Otx2, Brachyury, Sox17). After iPSC-CM differentiation, we confirmed the expression of prominent cardiac markers (CXN43, SERCA2a, GATA4 and cardiac Troponin T), as well as a lack of pluripotency markers (OCT4, Nanog, SSEA-4 and TRA-1-60) in the iPSC-CMs, via immunocytochemistry.

Results: Preliminary assessment of iPSC-CMs (days 1-20 post-differentiation) revealed significant baseline differences in beating rate ($p<0.01$) and contractility amplitude ($p<0.01$) between iPSC-CMs derived from cardiomyopathic patients and healthy donors. We then subjected iPSC-CM lines to hypoxic conditions (24 hours, 0% oxygen anaerobic chamber). Diseased patient-derived lines had significantly decreased viability and metabolic activity when compared to the controls, under normoxic ($p<0.01$) and hypoxic conditions ($p<0.001$). In addition, calcium imaging revealed differences between iPSC-CMs subjected to normoxic and hypoxic conditions.

Conclusions: Taken together, these results suggest that the detected differences at the cellular level after hypoxia-induced injury might be translatable to the inter-individual variability currently observed in the CVD patient population. With this, we hope to shift the focus towards these patient-specific cellular and functional differences, in the search for tailored therapies and a higher standard of care for CVD patients.

Effect of serum lipoprotein(a) levels on the progression to atherosclerotic cardiovascular disease in carriers of familial hypercholesterolemia variants

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Background: Serum lipoprotein(a) (Lp[a]) concentrations may contribute to the heterogeneity in the risk for atherosclerotic cardiovascular disease (ASCVD) seen in familial hypercholesterolemia (FH) mutation carriers.

Method: Using whole exome sequencing data on 193,310 individuals from the UK Biobank, we identified 1,189 carriers of putative FH variants with available longitudinal data for ASCVD and measured Lp(a) values. We compared the progression to ASCVD over a decade (mean follow-up time: 10.2 ± 2.3 years; 112 events) between FH carriers with normal serum Lp(a) concentrations (< 100 nmol/L, n = 942) and those with high Lp(a) concentrations (≥ 100 nmol/L, n = 247) using the Cox proportional-hazards model adjusted for age, sex, ancestry, and cholesterol-lowering medication use. A sensitivity analysis was performed to account for cholesterol-lowering medication.

Results: Compared to noncarriers, FH carriers have higher low-density lipoprotein cholesterol and apolipoprotein B levels and are likelier to use cholesterol-lowering medication. FH carriers with high serum Lp(a) concentrations developed ASCVD at a higher rate compared to those with normal Lp(a) levels in the whole study sample as well as in the subset of individuals (n = 816) not treated with cholesterol-lowering medication (hazard ratio [HR] [95% Confidence Interval (CI)] = 1.76 [1.18, 2.63], $p = 5.3 \times 10^{-3}$ for the total cohort; HR [95% CI] = 2.76 [1.54, 4.96], $p = 6.9 \times 10^{-4}$ for the untreated subset).

Conclusion: FH carriers with high serum Lp(a) levels developed ASCVD at a rate two-to-three times higher than those with normal Lp(a) concentrations. The ASCVD risk assessment for carriers of FH variants may be greatly improved by the inclusion of serum Lp(a) levels. Additional research should focus on the specific factors that contribute to the effect of high serum Lp(a) concentrations on increased ASCVD risk in FH.

Docetaxel is an anti-dyslipidemic and anti-atherogenic drug candidate

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Background. We have identified that a negative regulator of high-density lipoprotein (HDL) biogenesis, desmocollin 1 (DSC1) contributes to cholesterol accumulation in the atherosclerotic plaque. With screening of 10 million small molecules, the FDA-approved chemotherapy drug docetaxel was identified to inhibit the DSC1 activity and promote HDL biogenesis. To investigate whether docetaxel reduces atherosclerosis in an animal model, apoE-null mice were used.

Method. ApoE-null mice were fed a high-fat diet to promote dyslipidemia. After 2 weeks on the high-fat diet, one third of the mice were sacrificed as a baseline group. The rest were divided into two groups for subcutaneous implantation of an osmotic pump loaded with either 1 ug/ul of docetaxel or vehicle. The implanted mice were fed the high-fat diet for 6 weeks. At the end of 2 weeks (baseline group) and 8 weeks (docetaxel- and vehicle-treated groups), the mice were sacrificed for the analysis of blood and tissue samples.

Results. During the 6 weeks of docetaxel treatment using the osmotic pump, docetaxel concentrations in blood were maintained in the range of 2.7 – 4.3 nM, which is approximately 1,000 times lower than chemotherapy doses (1.9 – 5.1 uM) of docetaxel. A complete blood count test showed that the low nanomolar concentrations of docetaxel do not cause hematologic toxicity in apoE-null mice. Docetaxel reduced serum levels of triglycerides, non-esterified fatty acids, glucose, total cholesterol, LDL- and HDL-cholesterol. Docetaxel decreased all cholesterol in the serum, but increased the HDL-/total cholesterol ratio, which is consistent with docetaxel promoting HDL biogenesis. Measurement of the aortic surface area covered by lipid-laden atherosclerotic lesions showed anti-atherosclerotic effects of docetaxel: small lesions were observed in the baseline group and markedly increased in the vehicle group, but significantly reduced by docetaxel treatment.

Conclusion. These results demonstrate that docetaxel reduces atherosclerosis caused by dyslipidemia by decreasing atherogenic lipids (triglycerides, LDL- and total cholesterol), while increasing the HDL-/total cholesterol ratio in the blood. We strongly suggest that the DSC1 inhibitor, docetaxel may be used to treat atherogenic dyslipidemia and atherosclerosis.

Flexible Modeling of the Association Between Cumulative Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Hematopoietic Cancer in Children with Congenital Heart Disease

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Background: High-dose ionizing radiation is a well-established risk factor for childhood malignancies, including hematopoietic cancers (HC). However, data on the effect of low-dose ionizing radiation (LDIR) from medical imaging is conflicting and scant, especially in the pediatric population with congenital heart diseases (CHD). This study evaluated the association between cardiac LDIR exposure and hematopoietic cancers among children with CHD.

Methods: A nationwide population-based cohort study was conducted using the Canadian Congenital Heart Disease (CanCHD) database. The study population included children born between 1999 and 2017 with at least one CHD diagnosis in their medical records. The cumulative dose of ionizing radiation corresponding to cardiac diagnostic and therapeutic procedures was quantified considering a 6-month exposure lag. The recency-weighted cumulative exposure (WCE) model, a flexible extension of Cox's proportional hazards model, was used to assess the association.

Results: We identified 139,975 children with CHD born between 1999 and 2017 and followed them for 1,388,681 person-years since birth. In this population, 718 hematopoietic cancer cases were observed. Children with HC were exposed to low-dose ionizing radiation earlier in life (median age at first exposure: 6 vs. 10 months; $p=0.03$) and had more procedures than those without cancer (mean number of procedures: 0.4 vs. 0.2; $p<0.001$). The cases received higher cumulative LDIR doses than their counterparts (mean dose: 2.3 vs. 1.1 mSv; $p<0.001$). We observed that cumulative LDIR doses within five years were associated with increased risk of hematopoietic cancer with the maximum association magnitude around 2 years.

Conclusion: This is the first large population-based study documenting increased risk of HC associated with increased dose and recency of the LDIR exposure among children with CHD. Along with these findings, future studies focusing on detecting a threshold effect will help physicians decide the exposure point at which increased surveillance on LDIR exposure should be initiated.

Abstracts for Poster Presentations - Finalists

Multicomponent Geriatric Intervention for Frail Hospitalized Older Adults with Cardiovascular Disease: The TARGET-EFT Randomized Clinical Trial

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Background: During hospitalization for cardiac conditions, frailty can be exacerbated resulting in post-hospitalization syndrome and hospital-acquired disability. We hypothesized that a multicomponent geriatric intervention on targeting frailty deficits would improve health-related quality of life.

Methods: TARGET-EFT is a randomized clinical trial that enrolled patients ≥65 years of age with frailty (Essential Frailty Toolset (EFT) score ≥1) admitted to the cardiovascular ward at the Jewish General Hospital, an academic tertiary care center. The intervention group received supervised exercise training for physical weakness, reorientation and stimulation for cognitive impairment, nutritional optimization for malnutrition, and intravenous iron repletion for iron-deficiency anemia. The control group received clinical care as prescribed by their treating physicians. The primary outcome was health-related quality of life as measured by EQ-5D-5L scale and the main secondary outcome was hospital-acquired disability as measured by the Older Americans Resources and Services (OARS) scale ascertained by a blinded observer at 30 days post-discharge. Linear regression was used to determine the effect of our intervention on these continuous scores after adjusting for baseline health-related quality of life and disability.

Results: The intention-to-treat analysis included 142 patients with a mean age of 79.5 ± 7.8 years and 55% females. The mean EFT was 2.8 ± 1.1 at enrollment. Reasons for admission were heart failure (28%), ischemic heart disease (28%), arrhythmia (14%), valvular heart disease (11%), and other conditions (18%). Compared to usual care, the intervention led to clinically meaningful improvement in EQ-5D-5L score (Beta 0.08; 95% CI 0.01, 0.15; P=0.03; effect size 0.3) with no difference in basic and instrumental activities of daily living disability score (Beta 0.18; 95% CI -1.44, 1.81; P=0.82).

Conclusions: Our multicomponent geriatric intervention for frail older cardiac inpatients led to clinically meaningful improvements in health-related quality of life post-hospitalization. A more chronic intervention may be required to reduce hospital-acquired disability.

Pulmonary valve replacement in Tetralogy of Fallot: Risk of redo and comparison to the Ross procedure in a pan-Canadian study

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Background

Patients with Tetralogy of Fallot (TOF) commonly undergo a pulmonary valve replacement (PVR) as part of their treatment. Clinically, it is challenging to balance the benefits of redo PVR against redo PVR failure. The risk for redo PVR is understudied and poorly understood, often limited by a small sample size. Moreover, a comparison to other patient populations undergoing PVR has not been published. This study assesses the risk and risk factors for redo PVR in TOF in a pan-Canadian cohort and compares this risk to patients undergoing the Ross procedure.

Methods

Two databases, the Canadian Institute of Health Information (CIHI) and the Quebec ACHD databases, were integrated to create a pan-Canadian cohort. Patients who had a diagnosis of TOF were included. Patients who underwent a PVR after the age of 2 were assessed for an occurrence of a redo PVR. A Cox-regression analysis was preformed to assess the risk factors for redo PVR. A cohort of patients undergoing PVR as part of the Ross procedure was created separately, and risk of redo surgery was compared between the two cohorts.

Results

Out of TOF 4,746 patients, 1326 (27.9%) patients underwent a PVR. 408 patients had the PVR before the age of 2. Median follow-up time was 5.9 years. 79 patients (19.3%) underwent a redo PVR. The 5-,10- and 15-year risk of a redo PVR was 9.47%, 24.48% and 47.29%, respectively. Patients who underwent a redo PVR had their 1st PVR at a younger age (median age 8 Vs. 13 years, P<0.0001) and an earlier calendar year (2005 Vs. 2012, P<0.0001). In the Cox regression analysis, endocarditis before the 1st PVR (HR=5.55) and PR after the 1st PVR (HR=2.5) were found as risk factors for redo PVR. Patients were Compared to 167 patients who had the Ross procedure after the age of 2, with a median follow-up of 4.26 years. 15 patients (8.9%) underwent a redo PVR. The Ross procedure 5- and 10-year risk of redo PVR was 5.4% and 16.3%, respectively. The 10-year redo PVR risk in TOF was 50.18% higher than in the Ross population (24.48% Vs. 16.30%).

Conclusion

The rate of redo PVR in TOF patients is twice that of patient undergoing the Ross procedure. Although efforts have focused on improving the type of pulmonary valve used, our findings suggest that important anatomic features of the right ventricular outflow tract in TOF patients are at play.

Risk Factors Modify the Strength of a Coronary Artery Disease Genetic Risk Score

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Background: Coronary Artery Disease (CAD) is the leading cause of death worldwide and incurs a high societal burden. Genome wide association studies have identified many variants that contribute to CAD, although many have small effects. However, when these variants are combined into a genetic risk score (GRS), their sum demonstrates a stronger effect, which can improve the prediction of CAD. The strength and utility of a CAD GRS may not be the same across atherosclerotic risk factors.

Methods: A weighted GRS for myocardial infarction (MI) and CAD containing 204 single nucleotide polymorphisms (SNPs) was used to examine interactions with risk factors on CAD/MI in Cox proportional hazard analyses. We included 344,130 unrelated individuals of European ancestry from the UK Biobank with 23,752 incident CAD/MI events during a median follow-up time of 11 years. The GRS was first tested for association with CAD/MI in an age and sex adjusted model. We then examined interactions of the GRS with age, sex, hypertension, dyslipidemia, obesity, lipoprotein(a) levels, smoking and diabetes mellitus.

Results: The GRS was associated with CAD/MI (hazard ratio (HR) per standard deviation (SD) (95% CI), 1.37 (1.35,1.39); $P<2\times10^{-16}$). This GRS demonstrated interactions with age and sex; the effect on CAD/MI was higher in younger individuals ($HR_{interaction}$ per SD (95% CI), 0.95 (0.93,0.97), $P = 8.17\times10^{-8}$) and was increased in men compared to women ($HR_{interaction}$ (95% CI), 1.07 (1.04,1.11), $P = 5.00\times10^{-5}$). The GRS also interacted with diabetes and dyslipidemia: $HR_{interaction}$ (95% CI), 0.92 (0.88,0.97), $P = 1.20\times10^{-3}$ and $HR_{interaction}$ (95% CI), 1.05 (1.01,1.09), $P = 0.01$, respectively. The GRS had a higher HR in non-diabetics (HR (95% CI), 1.39 (1.36, 1.41), $P<2\times10^{-16}$ for non diabetics; HR (95% CI), 1.25 (1.20, 1.31), $P<2\times10^{-16}$ for diabetics) and in individuals with dyslipidemia (HR (95% CI), 1.40 (1.35, 1.45), $P<2\times10^{-16}$ for individuals with dyslipidemia; HR (95% CI), 1.34 (1.32, 1.37), $P<2\times10^{-16}$ for individuals without dyslipidemia). No interaction was observed between the GRS and hypertension, obesity, smoking or lipoprotein(a) levels.

Conclusion: A CAD/MI GRS demonstrated a stronger effect in men and in younger individuals. Our findings also showed interactions of this GRS with other atherosclerotic risk factors, namely diabetes and dyslipidemia. These results have important implications for the implementation of a CAD/MI GRS in routine clinical practice.

Apolipoprotein A-I carboxy-terminal domain residues 187-243 are required for adiponectin-induced cholesterol efflux

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Background: Adiponectin is a hormone that exerts its protective effects against atherosclerosis by inhibiting pro-inflammatory pathways. More recently, adiponectin has been shown to alter cellular lipid deposits by stimulating cholesterol efflux to lipid free apolipoprotein A-I (apoA-I). To this end, adiponectin has an emerging role in lipid metabolism, which may occur in part via activation of adenosine triphosphate binding cassette transporter A1 (ABCA1) and interaction with apoA-I. Previous evidence has demonstrated that the carboxy-terminal domain (CTD) region of apoA-I is essential for ABCA1 activity. However, the specific apoA-I CTD residues required for adiponectin-induced ABCA1-mediated cholesterol efflux has not been studied. Herein, we sought to determine the ability of adiponectin to bind apoA-I and to increase cholesterol efflux activity.

Methods: We performed cholesterol efflux from human Tamm-Horsfall 1 (THP-1) macrophages and Baby Hamster Kidney (BHK)-ABCA1 cells to observe adiponectin's potential to restore efflux in the presence of apoA-I and ABCA1 mutants, respectively. Lastly, we performed immunoprecipitation of apoA-I to observe binding of apoA-I or HDL to adiponectin.

Results: Adiponectin was unable to restore cholesterol efflux from THP-1 macrophages in the presence of apoA-I CTD successive mutants from residues 187-243 when compared to apoA-I mutants alone. Furthermore, the presence of adiponectin did not significantly influence cholesterol efflux to apoA-I from BHK-ABCA1 mutant cells. Immunoprecipitation of apoA-I demonstrated significantly higher non-specific binding of adiponectin to apoA-I 34.13±2.09% compared to HDL 12.66±1.40% ($p=0.01$). Similarly, in THP-1 macrophages, we reported significantly higher binding of adiponectin to apoA-I 43.24±3.00% compared to HDL 33.76±3.00% ($p=0.001$).

Conclusion: Adiponectin appears to require functional apoA-I CTD residues 187-243 for efficient ABCA1-mediated cholesterol efflux from THP-1 macrophages. Wild-type ABCA1 is required for adiponectin to mediate cholesterol efflux to apoA-I in BHK-ABCA1 expressing cells. Therefore, adiponectin cannot rescue impairment of cholesterol efflux in apoA-I- or ABCA1-mutant conditions, but rather increases cholesterol efflux in wild-type apoA-I conditions compared to apoA-I alone.

Genetic Testing for Familial Hypercholesterolemia in the Province of Québec: Update on a Retrospective Cohort Study

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Background: Familial Hypercholesterolemia (FH) is the most common genetic disorder in humans with a worldwide prevalence of 1/311 and up to 1/80 in geographic regions with founder effects as seen in Québec. FH is associated with premature atherosclerotic cardiovascular disease (ASCVD) caused by elevated low-density lipoprotein cholesterol (LDL-C). Although early diagnosis and therapy of FH can normalize life expectancy, less than 15% of cases are diagnosed. Cascade screening and genetic testing aim to improve diagnosis, treatment, and outcomes in FH.

Method: Here, we report a single center experience with the only CLIA compliant molecular genetic testing for FH in Canada at the MUHC. We performed next generation sequencing of the *LDLR*, *APOB* and *PCSK9* genes and multiplex ligation-dependent probe amplification (MLPA) of the *LDLR gene* to detect genetic mutations and copy number variants (CNVs). All mutations were reviewed by a geneticist and cross-referenced in ClinVar.

Results: Between 2018-2021, we examined 335 FH cases (55% males, 45% females) based on the Canadian definition of FH. For index patients, mean age at diagnosis was 42±16 years, while it was 30±17 years for cascade screening patients. Baseline (untreated) LDL-C was 7.0 ± 1.8 mmol/L. In 229 patients who underwent genetic testing, a pathogenic mutation was identified in 169 (74%) individuals, in keeping with ~20% of FH patients with a polygenic form. A large majority of affected patients had mutations in the *LDLR* (86%) or *APOB* (14%) genes. Interestingly, the genetic panel offered by Quebec's Health Ministry (MSSS), which includes 11 common mutations in French Canadians, only accounted for 49% of identified mutations. We subsequently examined the impact of genetic testing on re-classification of patients' FH diagnosis. Interestingly, 4 (31%) of patients initially classified as "severe hypercholesterolemia", and 90 (67%) of patients initially categorized as "probable FH" were re-classified as "definite FH".

Conclusion: Genetic testing in patients suspected of having FH provided diagnostic certainty and permits re-classification of individuals with a diagnosis of "severe hypercholesterolemia" or "probable FH" according to current definitions. Furthermore, the limited genetic panel offered by Québec, focusing on common French-Canadian mutations provides incomplete data in the majority of cases. We therefore propose that most patients with a presumptive diagnosis of FH undergo an unbiased genetic analysis. This study has implications on cascade screening, public health policies and reimbursement of drugs such as PCSK9 inhibitors.

Sex and body composition differentially impact the myocardial oxygenation response to breathing maneuvers

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Introduction:
Non-modifiable factors like age and sex, along with factors like body composition, impact vascular health. In healthy individuals, the impact of these factors on the microvasculature is unclear. Oxygenation-Sensitive Cardiac Magnetic Resonance (OS-CMR) is a validated methodology to examine vascular function using the breathing-induced myocardial oxygenation reserve (B-MORE). Previous OS-CMR research has observed a transmural gradient of blunted microvascular function in subjects with vascular risk factors but no overt cardiovascular disease (CVD). The aim of this study is to assess the impact of demographic factors like sex, age, and body composition on tissue oxygenation, as a marker of microvascular function, in healthy subjects. We hypothesize that these demographic factors will differentially impact B-MORE.

Methods:
We retrospectively assessed B-MORE in 105 healthy adults from 6 prospective OS-CMR studies, across 2 international study sites, Montreal (n=80) and Bern (n=25). Independent T-tests were used to view differences in microvascular function between the sexes and sites. ANOVA was used to view differences in microvascular function between age and CVD risk groups, and between myocardial layers. Linear regression was used to view the impact of individual factors on B-MORE. Principal component regression was used to assess the differential impact of all factors (age, sex, height, weight, heart rate, blood pressure, BMI, BSA) on B-MORE.

Results:
Male subjects showed significantly ($p<0.05$) greater mean B-MORE (8.509 4.068) compared to females (6.408 3.976). Subjects from Bern showed significantly ($p<0.05$) greater mean B-MORE (9.49) compared to Montreal subjects (6.70).Globally, B-MORE did not differ significantly between age or CVD risk groups. In linear regression analysis, subject height, BSA, heart rate, and sex impacted B-MORE ($p=0.03$, 0.01, 0.02, 0.006). In multivariable analysis, subject height, BSA, sex, and weight independently impacted B-MORE ($p=0.002$, 0.002, 0.01, 0.003). In subanalyses (n=80), B-MORE was homogeneous across endocardial and epicardial layers.

Conclusions:
Sex and body composition impact the microvasculature in the healthy population, improving our understanding of baseline variations in microvascular physiology. Further research is needed to clarify the impact of the environment/geography on B-MORE, which may be impacted by factors not assessed in this study.

Abstracts for Poster Presentations

(listed randomly)

Adherence, barriers and responses to cardiac rehabilitation: Are there differences between males and females?

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Background: In the past two decades, the prevalence of acute cardiovascular diseases (CVD) has increased, most notably in women, representing a growing worldwide health concern. Less women participate in cardiac rehabilitation (CR), despite being aware of its benefits on their overall quality of life. Therefore, barriers for women participation in CR are still unclear. We aimed at comparing the adherence, physical responses, main barriers and facilitators between men and women undergoing CR.

Methods: Preliminary data included males (n=15) and females (n=5) with acute CVD enrolled in a 12-week CR program at the Richardson Hospital between May to August 2021. Demographics and patient clinical characteristics, as well as exercise response measures including peak oxygen consumption (VO_2), 6-min walking test (6MWT) and Duke Activity Status Index (DASI) were collected. Questionnaires of exercise and CR barriers/benefits and facilitators were applied. Primary outcome measures included adherence rates to the CR program.

Results: Male and female population have similar age, socioeconomic status, ethnicity, as well as height, body mass index, left ventricular ejection fraction and blood pressure before and after CR. There were no significant differences in adherence rates to the CR program between males and females and on how positively they perceive exercise. However, male participants presented more significant positive physical responses to CR by increasing their peak VO_2 (22±5 pre vs. 33±4 post, ml/min/Kg, $p<0.0001$) and DASI (6.4±1.5 pre vs. 9.4±1.1 post, $p = 0.02$), while no significant changes were observed in peak VO_2 (24±8 pre vs. 30±5 post, ml/min/Kg, $p>0.05$) or DASI (6.8±2.3 pre vs. 8.8±1.6, $p>0.05$) in female participants. No differences were observed in 6MWT in both groups. Only females experienced lower anxiety and depression levels post CR. For the barriers to CR adherence, males indicated no energy and less motivation, while females identified weather, family, and work duties. Males additionally suggested an earlier enrollment to the CR program, while females suggested tele-rehabilitation programs to facilitate their adherence to CR.

Conclusion: Our preliminary results indicate that there is no significant difference in adherence between men and women participating in the CR program. However, we observed that male participants had more significant physical improvements than females. Flexibility in

methods of delivering CR, an earlier enrollment of the program and inclusion of tele-rehabilitation may lead to better adherence and responses to CR, particularly to women.

Novel Deep Learning Model for CT-Based Quantification of Frailty & Sarcopenia in Older Adults Undergoing TAVR

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Background
Frailty and sarcopenia are geriatric syndromes strongly associated with adverse outcomes in interventions such as transcutaneous aortic valve replacement (TAVR). There is a growing body of evidence in support of measuring ("segmenting") muscle mass and body composition on clinical CT images for risk stratification and pre-procedural optimization. However, manual segmentation is a tedious process that requires both expertise and time; in recent years, the advent of deep learning (DL) has presented opportunities to automate the workflow of image segmentation using deep neural networks.
UNet is a deep convolutional neural network designed specifically for medical image segmentation; however, the UNet architecture is not able to abstract knowledge about the relationships between distant regions of a CT slice, which we believe to be important in representing global body composition. The novel TransUNet model incorporates this important information into its architecture through its transformer architecture. In this study, we train the TransUNet model, and assess its performance against the benchmark UNet deep neural net.

Methods
We developed a body composition segmentation pipeline using TransUNet and UNet with the PyTorch framework on a GPU-enabled workstation. The dataset contained 386 CT slices at the L4 vertebral level extracted from pre-procedural clinical CT scans of older patients enrolled in the FRAILTY-AVR multicenter study. Fifteen percent of the CT scans were separated to form the test set. Hyperparameter grid search was applied to both TransUNet and UNet models to obtain the optimal configuration for each model. The DICE score was used for accuracy comparison between the models, capturing the similarities between the model's prediction and the ground truth body composition as segmented by trained readers.

Results
TransUNet outperformed the 2D-UNet in terms of segmentation accuracy by 3.0% DICE score in the test set (91.6% DICE vs. 88.6%). Moreover, TransUNet outperformed the 2D-UNet in terms of segmentation speed by 3x reduction in computation time on a per-slice basis (0.37s vs 1.1s).

Conclusions
TransUNet demonstrated superior performance for segmentation of body composition and diagnosis of frailty using clinical CT scans of older patients undergoing TAVR. Our TransUNet-

based pipeline achieved meaningful improvements in accuracy and speed, representing the current state-of-the-art for this predictive task.

Gendered Social Determinants of Health and the Risk of Thromboembolic Events and Bleeding in Atrial Fibrillation

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Background:
Atrial fibrillation (AF) is associated with an increased risk of thromboembolic events (TE) and bleeding. Balancing the risks and benefits of anticoagulation (AC) in patients with AF poses great challenges. Traditional risk factors have only shown moderate predictive ability for TE and bleeding outcomes. Whether social determinants of health (SDOH), which are gendered (i.e., diversity in the distribution between females and males), impact TE and bleeding in individuals with AF is unknown. We investigated if gendered SDOH are associated with TE and bleeding risk in AF.

Methods:
We used the EURObservation Research Programme (EORP) Long Term Registry, a multicenter, prospective, observational registry of Europeans with AF. Participants were recruited in 27 European countries from 2013 to 2016 and followed up to 2 years. Multivariate logistic regression models were used to assess the relationship between gendered SDOH (i.e., educational level, average national income per capita, domestic (marital) status, smoking, alcohol use, physical activity, EuroQoL 5D-5LT subscales), with a composite outcome of TE and bleeding (transient ischemic attack, peripheral embolism, pulmonary embolism, deep vein thrombosis and others), and major bleeding events. The data was split into 70% training and 30% test sets. Area under the curve (C-statistic) from the ROC curves was used to compare the discriminative ability of models with and without SDOH for predicting the outcomes.

Results:
From the 11,096 patients (mean age of 69.2 ± 11.41 years, 40.1% females, 85.1% with AC, 80% $CHA_2DS_2VASc \geq 2$), 9.45% had TE or bleeding during follow up. The multivariate model showed that higher income (OR: 0.48 (95%CI:0.37-0.61)), alcohol consumption (OR: 0.90 (95%CI:0.81-0.98)), greater health state at baseline (OR: 0.65 (95%CI:0.42-0.9)), AC (OR: 0.55 (95%CI:0.46-0.67) and CHA_2DS_2VASc (OR:1.09; 95% Confidence Interval (CI): 1.04-1.14) were significant predictors of TE and bleeding. The discriminative ability of our model with gendered SDOH improved (c-statistic: train set cross-validation 0.614, test set 0.629) as compared to the model with CHA_2DS_2VASc alone (c-statistic: train set cross-validation 0.552, test set 0.585).

Conclusions:
Gendered SDOH appear to be important predictors of clinical outcomes in patients with AF.

More research is needed to clarify how gender can be incorporated into clinical practice to better predict the risk of TE bleeding in this population.

Congenital Heart Disease: A Critical Review of Heart Failure Prediction Models

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Background:
The advent of innovative research studies has broadened our understanding of congenital heart disease (CHD). The focus of the management of CHD care has shifted to a longitudinal, individualized and lifespan approach. This motivates a need to better measure the evolution of CHD across the lifespan and to develop optimal tools to assess the risk of disease progression to inform management. The objective of this study is to review the current literature of heart failure (HF) predictive models pertaining to adult CHD patients and discuss future directions in methodology.

Method:
We focused on the computational models that were developed for adult CHD (ACHD) patients >=18 years of age with the objectives of predicting: (1) HF risk; (2) hospital readmission; (3) risk factors for the CHD-related adverse events. To comprehensively capture models for HF-related disease progression, results were organized chronologically to highlight the progression of the field and the limitations in the existing models. This motivates the implementation of new algorithms and techniques in subsequent studies. We also evaluated the interpretability of these HF models.

Results:
A total of 18 publications from 2006 to 2021 were identified and evaluated for this review. We categorized these studies into 3 categories of methodology: hypothesis-driven methods (n=8), regression-based methods (n=8), and deep learning models (n=2). Nearly half of them (n=8) are cross-sectional methods using aggregated information of electronic health records (EHRs). More recent studies have used longitudinal databases up to 28 years to model the progression of HF. In particular, a deep learning model predicted the 10-year HF and co-morbidity progression of ACHD. Three major limitations were recognized in these models: model design bias, accuracy, and interpretability. Of the 18 studies examined, 6 were found to have significant feature selection bias, 4 were found to have limited accuracy in their respective predictive task, and 3 were poorly interpretable models. In general, the increase of model complexity led to a decrease in model interpretability, especially for the deep learning models.

Conclusion:
Our findings indicate that the effective utilization of deep learning algorithms is a promising research direction to model the complex patterns of lifespan HF outcomes in adults with CHD.

Our finding also suggests that there is a need to create clinician-facing interpretable algorithms to facilitate their applications.

Automatic Detection and Characterization of Carotid Atherosclerotic Plaques from B-mode Ultrasound Images Using Deep Learning

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Background: Atherosclerosis in the carotid arteries is a main cause of cerebrovascular ischemic events, such as a transient ischemic attack or stroke. B-mode ultrasound serves as a safe, widely available, and cost-effective imaging tool that is readily used in clinical practice for detection and measurement of carotid atherosclerotic plaques, as well as the diagnosis for carotid endarterectomy (CEA). However, inter-user variability in the interpretation of ultrasound images and poor access to specialized expertise, particularly in remote or rural communities, has led to 1 in 10 patients being misdiagnosed and inappropriately treated. Therefore, there is a clinical need for a fast, accurate, and accessible approach to detect and characterize atherosclerotic plaques. To address this need, we propose an automatic and fast convolutional neural network (CNN)-based method to 1) detect and segment carotid atherosclerotic plaques from ultrasound imaging, and 2) quantify plaque morphology parameters, such as plaque thickness and plaque area.

Methods: Approval was granted by the McGill University Health Centre's Research Ethics Board. Patients with severe carotid atherosclerosis (n=131) underwent ultrasound imaging prior to CEA at McGill-affiliated hospitals. From these patients, a set of 429 ultrasound images including longitudinal (288) and transverse (141) images were anonymized (using in-house de-identification methods and processes). Manual annotations of the plaque border were performed by an expert radiologist, using Sedeen Viewer software, then converted to 2D masks. To develop plaque detection framework, CNN-based semantic segmentation model with a U-Net architecture was constructed. Patients were assigned to training (80%), validation (10%), and unseen testing (10%) groups. Rotations and modest scaling were used to augment the training set to 24425 images. Following CNN-based segmentation, the plaque thickness and area were automatically computed using conventional image processing methods.

Results: The intersection over union (IOU) between manual and algorithm-segmented plaque masks was 0.80 ± 0.21 on the unseen test set. The total computation time for plaque detection and measurements was less than 1 second per image.

Conclusion: We have developed a fully automatic system for 1) detection of carotid atherosclerotic plaques and 2) quantification of plaque thickness and area using ultrasound imaging comprising longitudinal and transverse images. The automatic deep CNN-based detection of atherosclerotic plaques achieved accurate results, which may be useful in clinical routine workflows in the future for better prediction of cerebrovascular risk.

IMPACT OF PHYSICAL FRAILTY ON SURVIVAL AND QUALITY OF LIFE IN HEART FAILURE PATIENTS

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Background: Frailty is prevalent in older heart failure (HF) patients and is associated with poor outcomes. There remains uncertainty on how to measure frailty in clinical practice, therefore, we compared the prognostic value of measures of physical frailty feasible in ambulatory HF clinics.

Methods: A multicentric prospective cohort study was assembled at 4 Quebec HF clinics. We assessed physical frailty using 3 scales: the Short Physical Performance Battery (SPPB), the Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire, and the Fried scale. Outcomes of interest were all-cause death or hospitalization at 3 months and quality of life using the 36-Item Short Form Survey (SF-36) questionnaire at 3 months. Multivariable logistic and linear regression models were employed and adjusted for age, sex, MAGGIC score, and SF-36 at baseline.

Results: The cohort included 215 patients with a mean age of 77.6 years. All three frailty scales were independently associated with death or hospitalization at 3 months; the adjusted odds ratios standardized per 1 standard deviation (SD) worsening of frailty were 1.67 (1.09, 2.55), 1.60 (1.04, 2.46), 1.55 (1.03, 2.35) for the SPPB, Fried, and SARC-F scales, respectively, with c-statistics of 0.77-0.78. The three frailty scales were independently associated with a decrease in the SF-36 score at 3 months; especially the SPPB for which each 1 SD worsening of frailty translated to a decrement of -5.86 (-8.55, -3.17) and -5.51 (-7.82, -3.21) points in the physical and mental component summary scores of the SF-36.

Conclusion: Physical frailty is associated with death, hospitalization, and reduced quality of life in ambulatory HF patients. While the SPPB showed slightly higher prognostic value, all 3 frailty scales can be efficiently used to predict adverse events in this setting.

The predictive value of the heart rate response to breathing maneuvers for significant coronary artery disease

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Background:
Simple breathing maneuvers (BM) with hyperventilation (HV) and breath-holds (BH), coupled with Oxygenation-Sensitive Cardiovascular Magnetic Resonance (OS-CMR) imaging, can reflect coronary vascular function. Recently, we could show that a blunted heart rate (HR) increase in response to HV may allow for identifying patients with cardiovascular disease. Our study aimed to assess the predictive value of the heart rate (HR) response to the BM for the presence of significant coronary artery disease (CAD).

Methods
We enrolled 56 patients with suspected CAD (age ≥ 35 years) and 14 age-controlled healthy controls. The CAD pre-test probability was assessed using validated European Society of Cardiology risk score. Using an FDA-approved EKG sensor, HR was recorded while performing a 4-min breathing maneuver that included 2 minutes of normal breathing (NB), followed by 1 min of deep and paced (30 RR/min) HV and a subsequent end-expiratory maximal BH. Significant CAD was defined as an inducible perfusion deficit in stress CMR perfusion or, in patients undergoing invasive coronary angiography evaluated by visual assessment. We calculated heart rate recovery during the breath-hold (HRR-BH, %) defined as HR recovery during BH relative to peak HR during HV ((Peak HR-HV – Min HR-BH/ Peak HR-HV) *100).

Results
Significant CAD was found in 39/56 patients (61±13 y, 46% female). Patients with coronary artery stenosis had a significantly lower HRR-BH (11.4%±6.5) than healthy controls (26.5±11.1%, p<.001) and patients without stenosis (20.6±14.9%, p=0.012). Men had a higher HRR-BH in both stenotic and non-stenotic groups, while women in the stenotic group had a greater HRR-BH. Overall, age showed a weak inverse correlation with HRR-BH in all participants (r=-0.3; p=0.011). An HRR-BH of ≥24% had a sensitivity of 97.4%, specificity of 35.2%, positive predictive value of 77.5% and negative predictive value of 85.7% (area under the curve 0.71). In patients with an intermediate (10%) and high (29%) pre-test probability of CAD, a negative likelihood ratio of 0.07 for HRR-BH ≥ 24% decreased CAD post-test probability to 0.77% and 2.7%, respectively.

Conclusion
In patients with suspected coronary artery disease, the heart rate recovery following a simple vasoactive breathing maneuver demonstrated a high negative predictive value for ruling out significant coronary artery disease. It may serve as a gatekeeper to improve patient selection for further diagnostic testing, specifically by correctly reclassifying patients with an intermediate or high pretest probability but a normal HR response from high-risk to low-risk. A larger prospective study is warranted.

Deep Learning-Based Segmentation of Atherosclerotic Plaque Features in Histopathology Images

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Background: Atherosclerotic plaques have a complex composition, consisting of inflammation, fibrosis, cholesterol crystals, hemorrhage, and/or calcification. The segmentation and quantification of plaque features in histopathology images form the foundation for studies evaluating plaque instability and the mechanisms that underlie the atherosclerotic process. Manual segmentation of plaque features from histology is a tedious, time-consuming, and subjective visual recognition task. We present a fully automatic approach using state-of-the-art deep learning techniques to identify several major features of the atherosclerotic plaque: calcification, lipid core, fibrosis, hemorrhage, and thrombus.

Method: Plaque specimens were collected from patients who underwent a carotid endarterectomy at McGill University-affiliated hospitals. Hematoxylin and eosin-stained sections were obtained from the region with the largest plaque burden, and whole slides were digitally scanned at 20x using a LEICA Aperio AT Turbo scanner. “Ground truth” annotations for all aforementioned plaque features were performed manually on whole section images of 70 plaques by three blinded cardiovascular pathologists using Sedeen Viewer software. For model development, a total of 23,000 512x512 pixel patches were extracted from these labeled images, and divided into the train (70%), validate (20%), and test (10%) sets. Using transfer learning, multi-class U-Net models for semantic segmentation were constructed and trained on the patches to identify calcification, lipid core, fibrosis, hemorrhage, and thrombus features. The mean intersection over union (mean-IOU) is used as a metric to describe the extent of overlap between the model segmentation and the ground truth and evaluate the model performance.

Results: The mean-IOU for each class was: lipid core = 0.78±0.03, calcification = 0.75±0.02, fibrosis = 0.77±0.02, hemorrhage = 0.60±0.03 and thrombus = 0.55±0.03. The model

performed better on the lipid core, calcification, and fibrosis than hemorrhage and thrombus possibly due to the greater prevalence of these features in our dataset. Overall, qualitative evaluation by pathologists suggested that the prediction results outperformed the ground truth. We are currently training our model using a larger dataset, and developing additional models for other plaque features, including neovascularization and fibrous cap.

Conclusions: We have developed a fully automatic approach for atherosclerotic plaque feature segmentation from histopathology images. Our models can accelerate atherosclerosis research, by improving the accuracy and speed of plaque analysis.

Homozygous Familial Hypercholesterolemia in Canada: Results from the HoFH Canada National Registry

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Background: Homozygous familial hypercholesterolemia (HoFH) is a life-threatening orphan disease characterized by high levels of low-density lipoprotein-cholesterol (LDL-C). Untreated patients often present with extensive xanthomas and marked premature atherosclerotic cardiovascular disease (ASCVD) before the age of 20. Prior to the advent of statins and extracorporeal LDL filtration techniques, survival beyond 30 years of age was unusual. Treatment with lipid-lowering therapy (LLT) is highly efficacious and has dramatically increased life expectancy, reducing the risk of ASCVD to background population rates. Canada is known to have several founder effect regions for HoFH, including Quebec.
Clinical outcomes in HoFH patients, especially ASCVD events such as myocardial infarctions or stroke are difficult to capture, in part because of the rarity of the disorder and the lack of registry focusing on this disease.

Methods: The objective of our project is to obtain a comprehensive registry of HoFH in Canada, estimate the cost to society caused by HoFH burden of disease in Canada, and implement changes to advocate access to specialized care for these patients. A standardized questionnaire was sent to the 19 academic sites across Canada participating in the FH Canada network. We previously identified 79 cases across the country, and have captured 46

of these cases. Here we describe their medical history, lipid levels, treatments and clinical outcomes.

Results: At the time of entry in the Registry, the mean age was 44 +/- 19 years, with a majority of females (54.4%), representing cases across 5 provinces. The average age of diagnosis was 16 +/- 4 years with 67.4% having untreated LDL > 10 mmol/L. Presence of physical markers, such as xanthomas or corneal arcus, were also found in 80.4% and 26.1% of patients, respectively. For LLT, 52.2% were undergoing LDL-apheresis, 91% were on statins and 41% on PCSK9 inhibitors. 54.3% displayed ASCVD, with 43.5% having aortic stenosis, 15.2% having experienced a myocardial infarction, and 36.9% having undergone one or more coronary artery bypass graft procedures.

Conclusion: We plan to use this data at provincial and national levels, helped by the Canadian Organization for Rare Diseases (CORD) and the Réseau Québecois des maladies orphelines (RQMO), to provide HoFH patients access to care, including orphan drugs such as evinacumab, and treatment techniques such as LDL apheresis. This work will provide important new health-related knowledge about the determinants of ASCVD risk and phenotypic manifestations of HoFH in Canada, and examine the quality of life and burden to the healthcare system.

The Impact of Sex and Gender-Related Factors on Length-of-Stay Following Non-ST Elevation Myocardial Infarction (NSTEMI): A Multicountry Analysis

Uri Bender[2], Rachel Dreyer[1], Colleen Norris[3], Harlan Krumholz[1], Valeria Raparelli [3]

Background: Gender-related factors are psycho-socio-cultural characteristics and are associated with adverse clinical outcomes in acute myocardial infarction (AMI), independent of sex. Substantial heterogeneity in hospital length-of-stay (LOS) exists among patients with non-ST-segment elevation myocardial infarction (NSTEMI). Whether sex and gender-related factors (e.g. employment, education, income) predict LOS among NSTEMI patients remains unknown.

Methods: Data from the GENESIS-PRAXY (n=1,210, Canada, U.S. and Switzerland), EVA (n=430, Italy) and VIRGO (n=3,572, U.S., Spain and Australia) cohorts of adults hospitalized for NSTEMI were analyzed. Baseline demographics and clinical characteristics were compared based on the overall median LOS (<4 days versus ≥4 days). A best-fit linear stepwise regression model, interaction and mediation analyses were performed to explore gender-related variables contribution to LOS .

Results: In total**,** 2,218 participants with NSTEMI were analyzed (66% females, mean age = 48.5±7.9 years, 67.8% U.S.). Individuals with longer LOS (51%) were more likely to be white and have diabetes, hypertension, and a lower income, while less likely to be employed and to have secondary education attainment. No univariate association between sex and LOS was observed. In the adjusted multivariable model, age (0.62 days/10 years, p<.001),

unemployment (0.63 days, p=0.01) and some of countries included relative to Canada (Italy=4.1 days; Spain=1.7 days; and the U.S.=-1.0 days, all p-value<.001) were independently associated with longer LOS. Past medical history mediated the effect of employment on LOS. No sex-by-employment interaction was observed.

Conclusion: Older age, unemployment and country of hospitalization were independent predictors of LOS, regardless of sex. Individuals employed with NSTEMI were more likely to experience shorter LOS. Cross-country variation in LOS across is likely due to institutional policy, resource allocation, and distribution of gendered factors.

Comparison of post-processing techniques for optimizing the quality of T1 mapping images

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Background: Myocardial T1 mapping is well established as a quantitative, non-invasive tool for myocardial tissue characterization[1]. Incidence of abnormal myocardium are common in patients with cardiomyopathies but may additionally stem from noise or anatomical misalignment due to motion[3]. The latter influences are not truly representative of abnormal myocardium, thus may result in falsely elevated T1 values and impair the image quality (IQ) of T1 mapping images. Two techniques--MOdified Look-Locker Inversion recovery with Motion Correction (MOLLI-MOCO) and MOLLI-MOCO with deep learning (MOLLI-MOCO-DL)--have been proposed to target these limitations[4,5].

Purpose: To compare the IQ and T1 values of T1 maps between conventional MOLLI, MOLLI-MOCO, and MOLLI-MOCO-DL.

Methods: 18 patients were scanned on a 3T SIGNA Premier (GE Healthcare, Milwaukee, USA). Three slices were acquired in the short-axis orientation using the MOLLI T1 mapping sequence. Images were further processed using both MOLLI-MOCO and MOLLI-MOCO-DL. The global and segmental myocardial T1 values were measured using cvi42 (Circle Cardiovascular Imaging Inc, Calgary, Canada) for each MOLLI, MOLLI-MOCO, and MOLLI-MOCO-DL using a blinded, cross-sectional analysis. An experienced reader also evaluated IQ using a 4-point Likert scale where 1 = non-diagnostic IQ, 2 = diagnostic IQ with many artefacts, 3 = few artefacts, and 4 = perfect IQ. Normal myocardial T1 values, locally obtained from a cohort of healthy volunteers, were used to classify segments of the myocardium as increased (greater than 2 SD), normal (within 2 SD) or decreased (lower than 2 SD)[2]. The Fleiss Kappa statistic was used to assess the similarity between the classification of the three methods.
Results: All 18 patients were successfully scanned, and their maps analyzed. An example of the T1 maps obtained using each method for one subject is shown in Figure 1. The MOLLI-MOCO and MOLLI-MOCO-DL techniques resulted in a higher IQ compared with MOLLI (Figure 2, A). All three methods had a reasonable agreement in the classification of myocardial tissue with a Fleiss Kappa score of 0.78. MOLLI-MOCO-DL and MOLLI-MOCO techniques

classified a greater number of segments as normal compared with MOLLI, indicating that they may suffer from fewer false positives than conventional MOLLI (Figure 2, B).

Conclusion: T1 MOLLI-MOCO and MOLLI-MOCO-DL improves IQ and classifies fewer segments as abnormal compared to MOLLI. Higher IQ is important for image analysis and for the robustness of T1 mapping evaluation. Further investigation into advanced motion compensation techniques is necessary to determine the robustness of their measured T1 values and their diagnostic accuracy.

The association between ER visits in any 1-year interval and mortality in heart failure patients

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Background:
Identifying heart failure patients with high risk of mortality may be helpful to guide therapy and assess prognosis. We sought to investigate whether the frequency of emergency room visits was associated with increased mortality in patients with heart failure.

Methods:
All patients followed at the MUHC Heart Failure Clinic between January 2000 and January 2020 were included in a registry. Patients with no echocardiogram in the electronic medical record and those with less than 1 year of follow-up were excluded, resulting in a total of 2476 patients and 16552 patient-years of follow-up. Emergency room (ER) visits, hospital admissions and mortality between their first evaluation at the heart failure clinic and December 2020 were obtained from the national health authorities (Institut de la statistique du Québec). We compiled the total number of ER visits (ERV) in every period of 1 patient-year and evaluated whether the number of ERVs was associated with mortality at the end of this 1-year interval. We also conducted the same analysis using only ER visits resulting in overnight stay in the ER, hospitalization or death (ERHD).

Results:
Baseline characteristics of the cohort are as follows: average age was 61.0 years, 71.4% were male, 47.1% had ischemic cardiomyopathy, and average LVEF was 33.7 %. NYHA class at baseline visit was: I: 24.8%, II: 58.5%, III or IV: 16.7%.
For the included 2476 patients, we compiled a total of 9449 ERVs, 5674 ERHD and 1057 deaths. The median follow-up time was 5.1 years (IQR 2.1 - 9.7 years). Median survival (Kaplan-Meier) was 9.6 years (IQR 3.7 - 18.2 years).
Patients with no ERV during any 1-year interval had a mortality rate of 3.8% during that year; those with 1 ERV had a 1-year mortality rate of 7.1% during that year; and 15.8%, 17.8%; 28.4%, 35.3%, 38.6% for 2, 3, 4, 5, and >5 ERVs in any one-year interval, respectively ($p < 0.0001$).
Even stronger statistical associations were found when restricting to ERHD: mortality rates

were 3.6%, 12.0%, 22.6%, 29.1%, 44.3%, 41.9%, 56% for 0, 1, 2, 3, 4, 5, and >5 visits in any 1-year interval, respectively ($p < 0.0001$; $p<0.05$ for all pairwise comparisons except between 4 and 5 ERHD).

Conclusion:
Emergency room visits in any given year is strongly associated to 1-year mortality during that year in patients with heart failure, particularly if emergency visits result in overnight stay or hospitalization.

Role of Sex and Gender in Development of Metabolic Syndrome: A Prospective Cohort Study

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Introduction:
The burden of metabolic syndrome (MetS) has been increasing mainly amongst men. Whether sex differences in the components and sequalae of MetS are influenced by psycho-socio-cultural factors (gender) is a matter of debate. We aimed to elucidate the role of biological sex and sociocultural gender in the development of MetS.

Method:
We used data from the Colaus/PsyColaus, a prospective population-based cohort of 6,734 middle-aged participants in Lausanne (Switzerland) (2003-2006). The primary endpoint was the development of MetS as defined by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) with the presence of ≥3 of the following risk factors: 1) waist circumference ≥102 cm for men and ≥88 cm for women; 2) elevated triglycerides (≥1.7 mmol/L);3) reduced HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women); 4) elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or use of antihypertensive drugs, and 5) elevated fasting plasma glucose (≥5.6 mmol/L) or medical treatment of hyperglycaemia] in either the first or second follow-up visits. Multivariable models were estimated using logistic regression to assess the association between gender-related factors and the MetS development.

Results:
Among 5,195 participants without MetS (mean age=51.3±10.6, 56.1% women), 27.9% developed MetS during a mean follow-up of 10.9-years. Female sex (OR:0.48, 95%CI:0.41-0.55) was associated with decreased risk of developing MetS. Conversely, advanced age (OR: 1.74, 95%CI: 1.40-2.18), high school, mandatory education and apprenticeship compared to university degree (OR: 1.91, 95%CI: 1.51-2.41), and low income (OR: 1.24, 95%CI: 0.99-1.56) were associated with an increased risk of MetS development independent of sex. We found

negative interactions between sex and strata of age, education and income regarding the risk of MeS. Indeed, the protective effect of female sex was diminished in women in the lowest education, income and advanced age strata. Conversely, there were positive interactions between sex and smoking and employment indicating that the protective effect of female sex was even stronger in women who smoke or are employed and smoking and unemployment were stronger risk factors in men than in women.

Conclusions:
Men had a higher risk of MeS but gender-related factors such as income and education played a more marked a role in the development of MetS in women than men. These factors represent novel targets for implementation of sex-specific clinical decision-makings to achieve health equity.

Performance Evaluation of Machine Learning Models for Prediction of In-Hospital Death in Patients Undergoing Aortic Valve Replacement

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Background
In patients undergoing surgical aortic valve replacements (AVR), traditional statistical models have achieved modest predictive accuracy for in-hospital mortality. In this study, we sought to determine whether contemporary methods can be improved upon using different machine learning models and to compare tree-based models versus neural networks.

Methods
This is a retrospective, multicentered study across Quebec and Alberta, Canada, of patients who underwent AVR with or without concomitant coronary artery bypass grafting (CABG) between 2009 and 2013. Data used in this study included demographics, medical history, surgical plan, angiography, and echography examination results obtained pre-operatively. Only data available until the commencement of surgery were used in our prediction models. All data was coded by trained personnel onto an online database. Missing continuous variables were imputed by IterativeImputer (RandomForestRegressor) for all models and up-sampling was done by Synthetic Minority Over-Sampling Technique (SMOTE).

Results
The study included 2418 patients, of whom 797 (32.9%) underwent AVR only, and 1621 (67%) underwent AVR + CABG. Mean population age for the whole cohort was 72.9 years (range: 38-93). Males comprised 68.9% of the cohort. In total, there were 65 recorded in-hospital deaths (2.67%). In-hospital death rate was 2.13% for patients undergoing AVR and 2.78% for patients undergoing AVR + CABG.
We compared in-hospital death prediction of Logistic Regression (LR), Random Forest (RF), XGBoost, and Multilayer Perceptron (MLP). The scores used were F1-score, area under curve (AUC), and sensitivity. Once the hyperparameters were optimized, the algorithm was run five times and the scores averaged. Across all models, the scores of up-sampled runs were noninferior to runs without up-sampling. Different imputation algorithms had no impact on prediction outcomes.
For LR, RF, XGBoost, and MLP, AUC scores were 0.73, 0.79, 0.75, and 0.77 respectively; F1-scores were 0.80, 0.90, 0.88, and 0.96 respectively; Sensitivities were 0.71, 0.71, 0.75, and 0.31 respectively.

Conclusion
Within our cohort, the in-hospital death rates are in line with the literature. Amongst our prediction models, given the difference in sensitivity, tree-based models are a more appropriate clinical tool for patient care in the post-operative setting. Amongst tree-based models, RF and XGBoost outperformed LR with a higher AUC and F1-score, where RF and XGBoost performed similarly.