
STEMI
WELLNESS
INTERDISCIPLINARY
CZT
IFNα-21
FLOWQUANT
CABG
GENETIC
BIOMATRIX
LIPID
9P21
PATIENT
STEM CELLS
CLINICAL
RUBIDIUM-82
REPAIR
X-RAY
EXCIMER
CMICE
INTERNATIONAL
HYPERTENSION
ARRHYTHMIA
CELLULAR
UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA
25th Annual Heart Institute
Research Day
Abstracts Program
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Foustanellas Auditorium
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Research Day 2012 Abstracts

May 7, 2012

BASIC SCIENCE ORAL PRESENTATIONS

O-1

A gain of function variant of the mitochondrial protease SPG7 is associated with increased risk of coronary artery disease.

Naif A.M. Almontashiri (Supervisor: Dr. Alexandre F.R. Stewart)

Background/Purpose: Mitochondrial ROS production plays a key role in the innate immune response. Inflammatory diseases, like coronary artery disease (CAD), are likely influenced by genetic variants that affect mitochondrial function. Here, we characterized a genetic variant (rs12960) that associates with the risk of CAD by meta-analysis of 12 GWAS in the CARDIoGRAM consortium. This variant replaces a conserved arginine at position 688 with glutamine (Q688) in the protease domain of the matrix AAA protease subunit encoded by SPG7. Together with the related protein AFG3L2, SPG7 forms a heterohexamer complex called mAAA protease that controls mitochondrial matrix protein synthesis and degrades misfolded proteins. SPG7 requires co-assembly with and processing by AFG3L2 to become proteolytically active.
Methods/Results: Using immunoblot, we found that processing of SPG7 to its mature and active form is regulated and inhibited by Forskolin in cell stably expressing the common form of SPG7. However, the Q688 variant escapes this regulatory process. Peripheral blood mononuclear cells from patients with CAD and primary human aortic smooth muscle cells that carry the Q688 SPG7 variant have more mature and active SPG7. Furthermore, using Electron micrograph and confocal imaging, we show that cells expressing this variant have increased mitochondrial fusion and numbers, produce higher levels of mitochondrial reactive oxygen species (mROS) and have increased cellular proliferation when tested using FACS analysis. ROS scavengers normalized markers of proliferation in these cells. Strikingly, when expressed in a yeast complementation experiment, the Q688 variant of SPG7 rescued the growth arrest caused by a protease-deficient mutation in AFG3L2 (E691K) known to cause cerebrospinal ataxia indicating that this variant is a gain of function.
Conclusion: My study identifies a novel functional variant of SPG7 that contributes to the risk of CAD by controlling mROS production and cell proliferation. Increased ROS production and cellular proliferation contribute to atherosclerotic lesion progression and would be expected to increase the risk of coronary artery disease.

O-2

Enhanced Matrix for Cardiomyogenesis and Regeneration of Infarcted Hearts

Nick Blackburn (Supervisor: Dr. Erik Suuronen)

Introduction: In cardiovascular disease, the repair response is insufficient to restore blood flow, leading to the death of muscle and loss of tissue function. Therefore, strategies to augment the endogenous cell response and its effects may help improve tissue recovery and function. In this study we explored the use of tissue engineered collagen matrices for augmenting endogenous regenerative processes after a myocardial infarct (MI).

Materials and Methods: Seven-to-eight week old C57BL/6J mice underwent LAD ligation to induce myocardial infarction. One week post-surgery the mice were treated via echo-guided injections with one of the following: i) PBS, ii) collagen matrix or iii) sialyl-lewis^X (sLe^X)-collagen matrix. Heart function was assessed by echocardiography at baseline (1-week post-MI) and at 4 weeks post-treatment. Mice were sacrificed, and cardiac tissue was harvested for immunohistochemistry, cytokine arrays and western blots.
Results: Mice treated with the sLe^X+collagen matrix had an improved ejection fraction (EF) of +2.5%±2% compared to the PBS group (-4.1%±1.1%; p=0.008), while the collagen-treated group had a preserved EF of +0.6%±1.9% (p=0.05). Immunostaining for arterioles showed that the vascular network was greater in matrix-treated groups (7.9±0.6 and 8.0±0.5 arterioles/FOV for collagen and sLe^X-collagen treated mice, respectively) compared to PBS (5.5±0.5 arterioles/FOV; $p\leq$0.004). Treatment with sLe^X-collagen matrix reduced apoptosis in the heart by 33% compared to PBS (p=0.02), as measured by active caspase-3 staining. The sLe^X-collagen matrix also reduced inflammation, as indicated by fewer CD68$^+$ macrophages (by 23%; p=0.03) and reduced inflammatory cytokine levels (e.g. IFN-γ, TNF-α; by ≥22%; p<0.05). Furthermore, the infarct area of the sLe^X+collagen matrix-treated group had a higher number of cells that expressed the cardiac stem cell markers c-kit (2.0±0.2) and Nkx2.5 (5.2±0.4), compared to PBS (1.5±0.1 and 2.5±0.7, respectively; $p\leq$0.02). As well, expression of the cardiac gap junction protein connexin43 was 1.4-fold greater in sLe^X+collagen matrix-treated mice compared to the other groups ($p\leq$0.0004).
Conclusions: Treatment with the sLeX+collagen matrix reduced inflammation and apoptosis and had a positive effect on endogenous regeneration and function of the infarcted mouse heart, through improved vascular density and possibly augmented cardiomyogenesis.

O-3

Coronary Endothelial Function Evaluated in Mice with [^{11}C]acetate PET Blood Flow Imaging

Etienne Croteau (Supervisor: Dr. Robert deKemp)

Objectives: Endothelial dysfunction (ED) is a common early symptom of hypertension, diabetes and atherosclerosis. The main function of the endothelium is to regulate the micro-vascular blood supply according to local changes in demand. We propose a hyperemic stress protocol with norepinephrine (NE) to derive the endothelial-specific myocardial flow reserve (EFR). The vasodilatation of the coronary microcirculation observed with myocardial PET perfusion imaging will be related to endothelial function.
Methods: In mice, the EFR was evaluated at two concentrations: 5.0 and 2.5 ug/kg/min i.v. over 10 min to optimize the appropriate norepinephrine (NE) dosage for infusion. A fiber optic sensor was placed in the carotid artery to measure peripheral blood pressure (BP) in healthy controls and in L-NAME (endothelial nitric oxide synthase inhibitor(eNOS)) pre-treated mice (drinking water 0.25mg/L for 1 week). PET imaging was conducted at baseline and following an optimized NE-stress protocol (radiotracer injection at 5 min) in C57BL mice (28 ± 1g). I.V. injection of 34 ± 16 MBq [^{11}C]acetate was used to measure myocardial EFR ratio (NE-stress: baseline).

Results: Overall, in control animals there was no change in heart-rate × systolic blood pressure product (RPP) ratio with (NE-stress:baseline); high dose was 1.26 ± 0.04 (N=3) and low dose was 1.23 ± 0.09 (N=5) ($p = 0.55$). L-NAME pre-treatment showed a significant decrease of the RPP ratio to 1.06 ± 0.03 (N=5) ($p<0.05$ vs. controls). A steady state BP response was typically reached after 2 min of NE infusion, and was sustained in both healthy controls and pre-treated mice. A 2-compartment model of [^{11}C]acetate kinetics was used to measure the EFR with FlowQuant© analysis of the PET images. Similar results were observed between the high dose and the low dose; the EFR values were 1.7 ± 0.3 (N=4) and 1.7 ± 0.8 (N=5), respectively. In mice pre-treated with L-NAME the EFR was 0.9 ($p<0.05$ vs. controls), reflecting a NE-specific effect of eNOS inhibition.
Conclusions: NE-stress induces a peripheral vasoconstriction, increasing the blood pressure by alpha-adrenergic stimulation, and dilating the coronary micro-vasculature by inotropic beta-adrenergic stimulation. The proposed [^{11}C]acetate NE-stress:rest protocol resulted in a positive EFR that was inhibited with L-NAME pre-treatment. This method for non-invasive investigation of endothelial function may be of interest in mouse models of disease and therapies affecting the coronary microvasculature.

O-4
Changes in cardiac sympathetic innervation and ubiquitin-proteasome system in rats after myocardial infarction.

Anastasia Drobysheva (Supervisor: Dr. Frans Leenen)

Increased cardiac sympathetic nerve activity (CSNA) plays a major role in the progression of heart failure after myocardial infarction (MI). Little is known about molecular mechanisms that underlie changes in cardiac sympathetic activity post MI.
Hypothesis: Increased CSNA post MI upregulates the expression of Tyrosine hydroxylase (TH) and Norepinephrine transporter (NET) in stellate ganglia (SG) and the heart and facilitates cardiac sympathetic axonal sprouting and hyperinnervation.
Objectives: To assess the time course of TH and NET gene and protein expression in SG and the heart at 1, 4 and 12 wks post MI and to assess changes in cardiac sympathetic innervation post MI.
Methods: Wistar rats underwent either coronary artery ligation or sham surgery. Mean MI size estimated by echocardiography was 35%. Gene and protein expression was assessed by RT-qPCR and Western blotting. Cardiac innervation density was assessed by fluorescent immunohistochemistry. Protein gene product 9.5 (PGP 9.5) and Growth associated protein 43 (GAP 43) were used as a neuronal markers to account for innervation density.
Results: At 1 wk post MI there was a significant 2 fold increase in PGP 9.5 protein expression in the base of left and right ventricles, and a significant 4 fold increase in PGP 9.5 protein expression in the peri-infarct LV area. These changes persisted at 4 wks post MI, but were no longer present at 12 wks. Cardiac myocytes rather than sympathetic axons were identified as a source of elevated PGP 9.5 expression. Since PGP 9.5 is an important enzyme in the ubiquitin mediated proteolysis, cardiac ubiquitin expression was assessed. Ubiquitin expression and ubiquitinated proteins in the heart were significantly increased 2 fold at 1 wk post MI as well. Sympathetic hyperinnervation notably increased GAP 43 immunoreactivity in the peri-infarct and infarct area acutely post MI. TH and NET protein expression in SG and the heart remained unaltered at all time points studied.
Conclusion: Increased CSNA post MI appears to have no effect on TH and NET expression in SG and the heart in rats at 1, 4 and 12 wks post MI. Expression of PGP 9.5 protein by cardiac myocytes and an increase in cardiac levels of ubiquitin and ubiquitinated proteins is consistent with an early dysfunction in the ubiquitin-proteasome system post MI.

O-5
Regulation of Low Density Lipoprotein (LDL) Receptor Degradation: The Effect of PCSK9-LDL Association

Mia Golder (Supervisor: Dr. Thomas Lagace)

Background: Proprotein convertase subtilisin/kexin type 9 (PSCK9) is a secreted protein that binds to the epidermal growth factor-like (EGF)-A domain of the low density lipoprotein receptor (LDLR) and mediates LDLR degradation in the liver. PCSK9 is abundant in human plasma, and its levels are positively correlated with LDL cholesterol. Previous size fractionation studies have shown that PCSK9 is partially associated with undefined high-molecular-weight complexes within the LDL-size range in human plasma. Thus, we hypothesized that PCSK9 interacts with LDL within the plasma, and this interaction regulates the degradation of liver LDLRs by PCSK9.
Results: *In vitro* binding studies showed an association between human LDL and fluorophore-labeled recombinant human PCSK9 but no interaction with VLDL. This interaction was competed >95% by excess unlabeled PCSK9, and homologous competition binding curves were consistent with a one-site binding model. LDL dose-dependently inhibited the binding and degradation of cell surface LDLRs by PCSK9 in HuH7 human hepatoma cells. This likely involves a non-competitive mechanism, as gel shift binding experiments showed that LDL and the LDLR EGF-A domain bind PCSK9 at non-overlapping sites. Approximately 40% of PCSK9 in pooled normolipidemic human plasma is associated with an LDL fraction isolated using iodixonal (Optiprep) density gradient. Immunodepletion of apoB in the same fraction resulted in the concomitant removal of PCSK9 from the fraction, confirming the interaction between PCSK9 and LDL.
Conclusion: The association of PCSK9 with LDL could modulate the ability of plasma PCSK9 to mediate the degradation of liver LDLRs.

O-6
[^{11}C]Methyl-EXP3174 as a Potential Radioligand for Imaging AT_1Receptor With PET

Basma Ismail (Supervisor: Dr. Jean DaSilva)

Introduction: AT1 receptor (AT_1R) expression is altered in cardiac and renal disorders. EXP 3174, a major downstream metabolite of the clinically used drug Losartan, has 10 times the affinity for the AT_1R as a reversible competitive antagonist than the parent compound. [^{11}C]methyl-EXP3174 was evaluated as a potential radiotracer for quantifying AT_1R.
Methods: Male Sprague–Dawley rats (n=4) were administered i.v. [^{11}C]methyl-EXP3174 (0.5 – 1.5 mCi) and imaged for 60 min with the Siemens Inveon MicroPET camera to evaluate tracer profile. Time activity curves were derived from the regions of interest (ROI) drawn from the reconstructed microPET images (Siemens IRW software). Distribution volume (DV) was quantified using Logan slope graphical analysis with the left atrial cavity used to obtain the

blood input function. Test-retest studies were conducted within 7 days to determine process reproducibility. Column switch HPLC with coincidence radioactivity detector was used to identify ^{11}C- labeled metabolites in rat plasma and kidney at 10 minutes.
Results: Kidneys showed high tracer uptake and SUV was 2.54 ± 0.83 with peak activity at 2 minutes and retained for 60 minutes. DV values were obtained from left kidney (2.19±0.6). Test-retest analysis showed a small variability and population variability was found to be 27.5 ± 0.27. HPLC analysis revealed 13 - 25% of total radioactivity signal in plasma derived from hydrophilic labeled metabolites. Whereas these radiolabeled metabolites accounted for 52 - 86% of the total signal in kidney.
Conclusion: In vivo studies support the use of [^{11}C]methyl-EXP3174 as an imaging agent to assess AT_1R in kidneys with good reproducibility. However, the presence of high proportion of metabolites in the target tissue is a potential problem. Further studies to assess the specific binding of the tracer and labeled metabolites are warranted.

O-7
A direct comparison of cardiac and blood stem cells reveals unique paracrine signatures with an equivalent capacity for myocardial repair

Nicholas Latham (Supervisor: Dr. Darryl Davis)

Stem cells hold the hope of mending the broken heart. Cell therapy with multiple cell types (including those that do not differentiate into new muscle) appears to be beneficial. Early attempts focused using blood derived endothelial progenitor cells (EPCs) has demonstrated these highly vascular cells restore perfusion and improve cardiac function after myocardial infarction through paracrine secretion and in the absence of significant engraftment, functional improvements are transient. Our lab has developed techniques to extract and grow cells directly from a patient's own heart biopsy with a view towards transplanting these cells back into damaged myocardium. We have shown these cells have a complementary repertoire of sub-populations that are capable of differentiating into cardiac lineage, secreting cardioprotective cytokines and improving post-ischemic cardiac function. Interestingly, the superiority of one cell type over the other has long been an area of speculation with no basic or clinical head to head trial ever being performed.
Methods and Results: Human left atrial appendages and blood samples were obtained from patients undergoing clinically-indicated heart surgery after informed consent. In hypoxic culture designed to mirror infracted myocardium, CSCs and EPCs provided a unique signature of pro-angiogenic and pro-cardiomyogenic growth factors. EPCs provided a more extensive paracrine profile than CSCs (5 vs. 14, respectively; $p<0.05$) including EGF and IGF-1, while CSCs secreted significantly higher amounts of angiogenin, IL-6, HGF, SDF-1α and VEGF ($p<0.05$).
Interestingly despite these differences, CSCs and EPCs demonstrated a similar capacity to promote the growth of vascular networks and to attract cell mediators of vascular repair. Twenty one days after transplantation into an immunodeficient mouse model of myocardial ischemia, CSC and EPC treatment provided identical improvements in echocardiographic left ventricular ejection fraction (+6.1±1.2 and 6.8±1.2%, respectively; $p<0.05$ vs. baseline) compared to negative cellular and saline controls (-7.7±0.7 and -6.7±2.5%, $p<0.05$ vs. either stem cell treatment).
Conclusions: CSCs and EPCs provide unique paracrine repertoires with equivalent effects on angiogenesis, stem cell migration and regeneration. The striking contrast between these paracrine profiles hints that combination therapy may synergistically enhance the revascularization effects of cell therapy.

O-8
Deregulation of E2F6 in Myocardium Induces miR-206 Leading to a Loss of Connexin-43 and Dilated Cardiomyopathy

Jennifer Major (Supervisor: Dr. Balwant S. Tuana)

Purpose: The E2F/Rb pathway is comprised of a dozen distinct proteins which are expressed in a cell/tissue specific context to regulate genes involved in proliferation, differentiation, and death. Perturbation of the E2F/Rb pathway through modulation of its members induces changes in the cell cycle which could potentially be targeted in cell growth and death. However, the constellation of E2Fs and Rb family members and their exact role in cardiac growth and development remains to be fully examined.
Methods: In order to modulate the E2F pathway *in vivo* in mouse myocardium, we expressed E2F6 (a transcriptional repressor of E2F responsive genes) under the control of the α-myosin heavy chain promoter. Microarray, microRNA array, and protein expression profiling were utilized to identify targets which were sensitive to E2F6 levels in transgenic (Tg) myocardium.
Results: E2F6-Tg mice presented with symptoms of Dilated Cardiomyopathy (DCM) which led to early mortality. Microarray analysis revealed that E2F responsive transcripts involved in cell cycle regulation including E2F1 and E2F3 were up regulated in Tg hearts (~19 and 3 fold respectively). Although these and thirty other cell cycle genes were up-regulated they did not induce any changes in cardiomyocyte size or number. Surprisingly, western blot analysis indicated that E2F1 protein levels were unchanged and E2F3B was down-regulated by ~60%, implying a post-transcriptional control mechanism for E2F6 which may contribute to the lack of effects on cardiomyocyte growth Tg hearts. microRNA array detected the induction of non-cardiac specific microRNAs including neuronal enriched miR-124 which was up-regulated by ~2 fold, and a robust 10 fold increase in the skeletal muscle enriched miR-206. Activation of miR-206 was linked to a post-transcriptional loss of the gap junction protein, connexin-43(~75% loss) and abnormal electrocardiogram in Tg mice. We also noted a specific activation of the Extracellular Receptor Kinase (ERK) which has been linked to the induction of miR-206 and a loss of connexin-43. The DCM noted in E2F6-Tg mice is similar to that initiated by mutations in nuclear proteins which are associated with the inappropriate docking of Rb and activation of E2F responsive transcripts as well as ERK activation and a loss of connexin-43.
Conclusions: This study demonstrates a previously unrecognized role for E2F6 as a transcriptional activator and as a post-transcriptional regulator of gene expression *in vivo*. Further, the data suggest that a strict control of the E2F pathway by a subset of E2Fs is critical for normal cardiac development and function.

O-9

Collagen matrices enhance circulating angiogenic cell function through the integrin receptors

Brian McNeill (Supervisors: Dr. Marc Ruel and Dr. Erik Suuronen)

Purpose: We have demonstrated that culturing peripheral blood mononuclear cells on a collagen-based matrix enhances their therapeutic potential. The aim of this study was to investigate the involvement of integrin proteins in regulating the various collagen-mediated cellular processes that lead to the therapeutic enhancement.
Methods: The expression of several different integrin genes (18 α- and 8 β-integrins) was evaluated in $CD34^+$ circulating angiogenic cells (CACs) following 2, 4 and 7 day culture of human peripheral blood mononuclear cells (PBMCs) on fibronectin or collagen matrix. $CD34^+$ cells were collected by fluorescent-activated cells sorting and integrin expression measured using quantitative RT-PCR. Positive findings were further investigated using specific integrin blocking antibodies and small molecule pathway inhibitors. The effects of these blocking antibodies and inhibitors on collagen matrix-cultured CACs were evaluated by characterizing the phenotype of these cells, examining the effects on cell adhesion and by evaluating the angiogenic potential of these cells.
Results: Culturing peripheral mononuclear cells on the collagen-based matrix significantly increased the proportion of $CD34^+$ cells compared to fibronectin. The integrin profile between the fibronectin- and collagen-cultured cells was significantly different: integrins α5, α7, αV and β3 were up-regulated greater than 50-fold in collagen-cultured $CD34^+$ cells, while integrin α3 and β7 were down-regulated by 30- and 60-fold, respectively. When PBMCs were cultured on collagen matrix in the presence of the integrin α5 blocking antibody, the proportion of $CD34^+$ and $CD133^+$ CACs was significantly increased over both fibronectin and collagen alone. Examining potential downstream integrin signaling mechanisms, the use of inhibitors to block the ERK/MEK pathway resulted in similar increases in $CD34^+$ and $CD133^+$ CACs as was seen with the α5 blocking antibody. Functionally, the PBMCs demonstrated increased adhesion when the ERK/MEK pathway was inhibited and an increase in their angiogenic potential when integrin α5 and ERK/MEK were blocked.
Conclusions: Collagen matrix culture of PBMCs significantly increases the proportion of $CD34^+$ CACs, possibly through the regulation of specific integrins. We demonstrated that blocking the activity of integrin α5 significantly increased the proportion of $CD34^+CD133^+$ CACs, suggesting that this integrin may be a negative regulator of these progenitor cells, possibly through the activation of the ERK/MEK pathway.

O-10

Hematopoietic Over-Expression of Heat Shock Protein 27 is Atheroprotective and Extracellular Heat Shock Protein 27 Signals Through NF-kB to Favorably Modulate Macrophage Inflammation

Tara Seibert (Supervisor: Dr. Edward O'Brien)

Purpose: Heat Shock Protein 27 (HSP27) is a biomarker for CAD, and reduced expression of HSP27 correlates with the extent of atherosclerosis in human coronary arteries. Moreover, over-expression of HSP27 can attenuate atherogenesis in $ApoE^{-/-}$ mice. The purposes of this study were i) to determine the cell type(s) responsible for HSP27 atheroprotection, and ii) assess the signaling mechanisms involved in atheroprotection.
Methods/Results: Bone marrow was transplanted from an HSP27 over-expressing mouse strain ($ApoE^{-/-}HSP27^{o/e}$) into atheroprone $ApoE^{-/-}$ mice resulting in markedly elevated circulating HSP27 levels (588 ± 203 pg/ml). Notably, this increase in serum HSP27 was sufficient to reduce atherogenesis in both the *en face* and aortic sinus lesions (50% and 28% respectively, $p=0.002$ for both). Furthermore, histomorphological analysis of the aortic sinus lesions revealed a 49% ($p<0.001$) reduction in the non-necrotic lesion core area and a 59% decrease in the apoptotic intimal cell area ($p=0.007$). Mechanistically, we observed that rHSP27 was able to activate NF-κB signaling in peritoneal macrophages from $ApoE^{-/-}$ mice. Treatment with rHSP27 (9.6 μM) for 30 minutes increased translocation of the NF-κB p65 subunit from the cytosol to the nucleus. To quantify this effect, a dose dependant increase in rHSP27 mediated NF-κB activation was observed in RAW 264.7 macrophages stably transfected with an NF-κB inducible reporter gene (up to 10 fold induction vs. control; $p<0.05$). The use of an N-terminal deletion mutant of rHSP27, rC1, was not able to induce NF-κB activation, demonstrating specificity of the full-length protein. Additionally, BAY 11-7082 and MG-132, known inhibitors of NF-kB signaling, were able to attenuate the induction of the NF-kB reporter gene by HSP27. Unbiased assessment of mRNA transcripts was performed using qPCR arrays. Several known NF-KB target genes were up-regulated including a marked up-regulation of the transcript for the haematopoietic growth factor/regulator, GM-CSF (300 fold; $p<0.05$). This up-regulation was NF-KB specific as both BAY 11-7082 and MG-132 reduced this effect.
Conclusions: Over-expression of HSP27 in hematopoietic cells is sufficient to achieve therapeutic HSP27 levels and provide atheroprotection in $ApoE^{-/-}$ mice. Extracellular rHSP27 promotes the nuclear translocation and activation of NF-κB which results in the up-regulation of numerous gene transcripts that may be responsible for the observed therapeutic effects *in vivo*. This data suggests that HSP27 modulation of macrophage NF-KB signaling may be central in the observed atheroprotection.

O-11

The intracellular redox state is a core determinant of mitochondrial fusion

Timothy Shutt (Supervisors: Dr. Ross Milne)

Purpose: Mitochondrial dynamics have recently been recognized as playing an important role in cardiac function and protection form cardiac injury. It has been observed that several different cellular stresses result in mitochondrial fusion and fusion has been demonstrated to be protective against cell death. Here, we investigate the basic mechanisms controlling mitochondrial fusion in response to stress. A better understanding of the cell's response to oxidative stress is crucial to improving the treatment of heart disease and cardiac injury, where oxidative stress plays an important role.
Methods: We have developed a bimolecular complementation approach that follows the re-assembly of luciferase upon the mixing of mitochondria *in vitro*. This robust assay allows us to quantify

mitochondrial fusion independently of fission, enables us to stage the mitochondrial fusion reaction under various conditions and also facilitates biochemical analysis. Furthermore, standard *in vivo* analysis of mitochondrial morphology is also performed to confirm our findings.
Results: We demonstrate that the redox status of the cell regulates mitochondrial fusion. *In vitro* and *in vivo* analyses demonstrate that oxidized glutathione, the cell's primary indicator of oxidative stress, strongly induces mitochondrial fusion. The stimulation of mitochondrial fusion is accomplished mechanistically through the formation of intermolecular disulfide bonds of the mitochondrial outer membrane proteins Mitofusin1 and Mitofusin2, which are required for mitochondrial fusion. We also show that the GTPase activity of these proteins is required for the formation of these disulfide oligomers and propose a model of how mitochondrial fusion is regulated.
Conclusions: While many types of regulation have been reported for the process of mitochondrial fission, this is the first insight into the mechanistic regulation of the mitochondrial fusion process. We observe that both redox and nucleotide state play a role in oligomerization of mitofusins and ultimately fusion. Altogether, our results provide novel evidence for the mechanistic regulation of mitochondrial fusion in response to changes in the redox status of glutathione in the cell. Ultimately, mitochondrial dynamics may prove to be a therapeutic target which modulates cell survival outcomes in response to cardiac stress.

O-12
Functional Relationship of the *COL4A1/COL4A2* Locus on Chromosome 13q34 to Coronary Artery Disease (CAD)
Adam Turner (Supervisor: Dr. Ruth McPherson)

The *COL4A1* and *COL4A2* genes on chromosome 13 have been identified as new loci associated with CAD ($p<3x10^{-8}$) from the recently published CARDIoGRAM study (*Nature Genetics*, 2011). The CARDIoGRAM study is a large meta analysis of genome-wide association studies for CAD (>22,000 CAD cases & >64,000 controls) that overall discovered 13 novel regions associated with CAD. The index SNP at the *COL4A1/COL4A2* locus from the CARDIoGRAM study (rs4773144) has a minor allele frequency of 0.4 and is associated with an increased risk of CAD (allele specific odds ratio=1.21 in the Ottawa Heart Study (OHS)). The goal of the current project is to elucidate how variants in the *COL4A1* and *COL4A2* genes associated with CAD functionally and mechanistically contribute to the CAD phenotype. Type IV collagen triple helices constitute the major structural component of basement membranes, consisting primarily of 2 COL4A1 chains arranged with 1 COL4A2 chain. *COL4A1* and *COL4A2* also have important functional roles in angiogenesis, and mutations are associated with diverse vascular abnormalities. In a search for functional genetic variants, we resequenced the bidirectional *COL4A1/COL4A2* promoter in 500 CAD cases and 500 controls and identified four novel SNPs, in promoter/enhancer regions essential for *COL4A1* and/or *COL4A2* gene expression and in strong linkage disequilibrium with several OHS risk SNPs. Three of these novel SNPs are in the region necessary for *COL4A2* transcription and in promoter luciferase assays with HT-1080 cells result in 15-20% decreases in *COL4A2* promoter activity ($p<0.005$). Furthermore, a follow-up study to CARDIoGRAM with more cases and controls has identified an intronic SNP in *COL4A2* with an even higher CAD association than rs4773144. 2 kb of this intronic sequence containing the CAD-associated SNP was cloned into the pGL3-Promoter vector (Promega), in which insertion of functional enhancers leads to upregulation of luciferase expression *in vitro*. Luciferase assays in HT-1080 cells reveal this intronic sequence acts as an enhancer due to its insertion upregulating pGL3-Promoter activity over threefold relative to controls. Future work entails narrowing down what SNP(s) in this enhancer region has actual functional consequences (ie. disrupting transcription factor binding sites). We also plan on conducting chromosome conformation capture experiments to determine whether this enhancer acts locally on *COL4A1/COL4A2* or acts long-range on other genomic targets. These findings are important because misregulation of *COL4A1* and *COL4A2* could have important consequences relevant to CAD, including effects on basement membrane integrity and angiogenesis.

CLINICAL SCIENCE ORAL PRESENTATIONS

O-13
Acutely Symptomatic High-risk for Stroke Patients have Greater Internal Carotid Artery Inflammation: Insights from FDG-PET Imaging - A FDG PET sub-study of the Canadian Atherosclerosis Imaging Network (CAIN)
Myra Cocker (Supervisor: Dr. Rob Beanlands)

Background: With rising obesity and diabetes pandemics, atherosclerotic disease is expected to become a global cause for disease by 2020. Vulnerable or rupture-prone plaque consists of increased inflammatory burden, especially macrophage cell expression. Macrophages are highly metabolically active cells that can probed with [18F]-fluorodeoxyglucose (FDG), given that FDG is a radiolabelled glucose analogue. Evidence suggests that the uptake of FDG in atherosclerotic plaque is a marker of active inflammation within plaque, and can therefore non-invasively identify vulnerable lesions. However, the relationship between symptomatic patient presentation and plaque inflammation is not well understood. Hence, in this study, we sought to assess whether the presence of acute symptoms in patients at high risk for developing stroke is associated with inflamed plaque, as demonstrated by FDG uptake.
Methods: 25 patients (65±9 years, 19 male) scheduled for carotid endarterectomy were prospectively recruited. A threshold of 6 months was implemented to define patients as acutely symptomatic or asymptomatic. Patients presenting at less then 6 months from the last reported symptom were classified as "acutely symptomatic". Patients whose last reported symptom occurred more then 6 months prior to the imaging protocol or who had no reported symptoms were categorized as "asymptomatic". Patients underwent hybrid FDG PET/CT imaging of carotid vasculature and maximal FDG uptake was quantified using a tissue to blood ratio (TBR) in internal carotid artery vasculature.
Results: Amongst the 25 patients in this study, 15 were classified as acutely symptomatic (average duration from last reported symptom 53±40 days) and 10 were classified as asymptomatic (5 were completely asymptomatic patients with no known symptoms and 5 with last reported symptom occurring 1008±1287 days prior to

imaging). Of 50 bilateral internal carotid artery lesions, 49 were evaluable. FDG uptake in carotid lesions from acutely symptomatic patients was greater then that in asymptomatic patients (3.3±2.2 TBR acutely symptomatic vs. 2.3±0.5 TBR asymptomatic, p=0.043).
Discussion and Conclusion: Findings from this investigation suggest that acutely symptomatic patients have greater internal carotid artery inflammation then patients who are asymptomatic. Furthermore, although patients were unilaterally symptomatic, there is evidence for bilateral inflammation which lends support to the concept of a ***"vulnerable patient"***. Insight on inflammatory burden and its association with patient symptoms may be used to triage patients.

0-14
Quantitative Scar Imaging using Multislice Computed Tomography
Girish Dwivedi (Supervisor: Dr. Benjamin Chow)

Purpose: F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is an established metabolic imaging technique to assess myocardial viability. Delayed iodinated contrast enhancement (DE) of myocardium on multislice computed tomography (CT) has also been shown to be an anatomical marker of non-viable myocardium. A proof-of-concept study was undertaken to determine quantitative and qualitative agreement between metabolic viability imaging and scar imaging using FDG PET and CT respectively.
Methods: Fifteen patients with coronary artery disease and left ventricular dysfunction were recruited in the study. All patients underwent same day FDG PET and DECT to evaluate myocardial viability. The images were analyzed quantitatively and qualitatively using a 17 segment model.
Results: DECT diagnosed viability in 57% (146/255) whilst PET in 51% (129/255) of segments. The per-segment agreement between DECT and FDG PET on qualitative analysis was 70% (Kappa: 0.40). The agreement in quantitative measurements between the two techniques for viability showed good correlation [Pearson ρ:0.63; P<0.0001] on scatter plot and the Passing-Bablok regression analysis. Higher agreement (70 vs 77%; P=0.051; Kappa: 0.40 vs 0.53) were obtained with quantitative compared to qualitative DECT.
Conclusions: DECT may be useful in characterising myocardial scar, and preliminary results correlate well with metabolic FDG PET, both qualitatively and quantitatively. Although in our study quantitative analysis offered superior agreement compared to qualitative with DECT, further studies are needed to determine its incremental value.

O-15
Double Valve Replacement: Biological versus Mechanical Prostheses
Elsayed Elmistekawy (Supervisor: Dr. Marc Ruel)

Background: Only scarce data are available regarding outcomes after double valve replacement (DVR). A knowledge gap exists and customary age recommendations for the use of biological versus mechanical prostheses may not apply. We examined the early and late results of DVR in the largest series so far available.
Methods: We studied 319 patients who had first time DVR after 1980. Patients were followed in a dedicated valve clinic. Mean follow-up was 6.3±6.0 years. Semiparametric time-to-event analyses were used to assess outcomes and risk factors.
Results: Age at surgery was 63.1±12.8 years, and 185 patients (58.0%) were female. Two mechanical prostheses were used in 168 patients (52.7%), 2 biological in 149 (46.7%), and a mixed combination in 2 (0.6%). There were 34 perioperative deaths (10.8%), and 35 patients required reoperation at a mean of 7.2±4.8 years (hazard ratio 6.1±2.3, $P<0.0001$, biological versus mechanical). Accounting for age and gender, the use of 2 biological prostheses was associated with a strong trend towards higher late mortality (hazard ratio (HR) 1.6±0.4; $P=0.05$). A hazard inflection point occurred at age 72, with patients 71 years old or younger treated with 2 biological prostheses having an increased risk of late death (HR 2.0±0.5; $P=0.008$), while those 72 or older did not (HR 1.2±0.6; $P=0.7$).
Conclusions: Double valve replacement carries significant risk, both early and late postoperatively. Reoperation is frequent, and the use of biological prostheses is preferably avoided in patients less than 72 years, unless strong patient preference or a specific indication exists.

O-16
Bivalirudin for Primary Percutaneous Coronary Interventions: Outcome Assessment in the Ottawa STEMI Registry
Benjamin Hibbert (Supervisor: Dr. Michel Le May)

Background: Randomized data has demonstrated the superiority of bivalirudin to GPI *plus* heparin in patients undergoing primary percutaneous coronary intervention (PPCI). Real-world performance of bivalirudin in PPCI and the benefit of bivalirudin over heparin remains unknown in an era of routine dual antiplatelet therapy.
Methods and Results: From July 2004 to December 2010, 2317 consecutive patients were indexed in the University of Ottawa Heart Institute STEMI registry. During this period 748 patients received bivalirudin, 699 patients received GPI, and 676 patients received unfractionated heparin alone. The primary outcome was the rate of non-coronary artery bypass graft (CABG) related Thrombolysis In Myocardial Infarction (TIMI) major bleeding. Bivalirudin significantly reduced the primary outcome compared to heparin plus GPI (2.7% vs 7.3%, adjusted OR 2.78, 95% CI 1.53-5.06, p<0.001). A strong trend towards a reduction in the composite endpoint of death, stroke, re-infarction and major bleed was also seen between bivalirudin and GPI (OR 1.49, 95% CI 0.98-2.28, p=0.06). Compared to heparin alone, bivalirudin failed to reduce major bleeds (OR 1.15, 95% CI 0.59-2.24) *or* the composite endpoint (0.97, 95% CI 0.62-1.51).
Conclusions: Bivalirudin use compared to GPI plus heparin as an antithrombotic strategy in PPCI results in less major bleeding in contemporary practice. A benefit of bivalirudin over heparin alone was not observed and remains to be established.

O-17
Functional Significance of Recurrent Mitral Regurgitation after Mitral Valve Repair for Ischemic Mitral Regurgitation
Andranik Petrosyan (Supervisor: Dr. Marc Ruel)

Background: Controversy exists as to whether moderate mitral regurgitation (MR) that persists or recurs after mitral valve repair for ischemic MR (type IIIb) is associated with functional consequences.

This issue, which has not formally been studied before, carries heightened relevance in the context of new percutaneous mitral interventions that result in a relatively high incidence of MR post-procedurally.
Methods: We followed-up and studied 92 patients who had mitral valve repair for MR caused by posterior leaflet restriction ± annular dilatation. Patients were seen annually in a dedicated valve clinic, and underwent serial echocardiograms. Mean follow-up was 2.5 years (maximum 8.6 y). Ordinal logistic regression was used to examine whether a correlation existed between functional status and persistent/recurrent MR postoperatively, while adjusting for age and follow-up duration.
Results: Mean age was 65.7 ± 9.1 years, and 21 patients (23%) were female. Preoperatively, 52 patients (57%) were in NYHA functional class III or IV, and all exhibited some degree of left ventricular dysfunction. At surgery, ring or band annuloplasty was performed (median size 28mm), and supplemented with edge-to-edge repair in 44 patients (48%). There were no operative deaths. At latest follow-up, 8 patients (9%) were in NYHA class II or III, and echocardiography indicated that 22 patients (24%) had 1+ MR, and 10 (11%) had 2+ MR. There was a strong trend for patients with recurrent MR to experience worse functional status postoperatively (odds ratio 2.6 ± 1.3 per increasing postop MR grade; $P = 0.07$).
Conclusions: After mitral valve repair for ischemic MR, persistent or recurrent MR of mild to moderate degree appears associated with functional compromise. This finding carries implications with regards to the ongoing controversy of mitral valve repair versus replacement for ischemic MR, and for new percutaneous mitral therapies which may not eradicate MR.

O-18
Point-of-Care Genetic Testing for Personalization of Anti-Platelet Therapy: A First Description in Clinical Medicine
Jason D. Roberts (Supervisor: Dr. Derek Y. F. So)

Purpose: Prospective evaluation of pharmacogenetic strategies has been limited by an inability to perform genetic testing at the clinical bedside. The *CYP2C19*2* allele is a common genetic variant associated with increased rates of major adverse events following percutaneous coronary intervention (PCI) in individuals receiving clopidogrel. We utilized a novel point-of-care genetic test to identify carriers of the *CYP2C19*2* allele and evaluated a pharmacogenetic approach to dual anti-platelet therapy following PCI.
Methods: We randomly assigned 200 patients undergoing PCI for acute coronary syndrome or stable angina to a strategy of rapid point-of-care genotyping with selective administration of prasugrel to *CYP2C19*2* carriers or to standard therapy with clopidogrel 75mg daily. The primary endpoint was the proportion of *CYP2C19*2* carriers with high on-treatment platelet reactivity, a marker associated with increased adverse cardiovascular events, in the rapid genotyping arm compared to those in the standard therapy arm.
Results: The point-of-care genetic test exhibited a sensitivity of 100% (95% confidence interval [CI]: 92.3-100%) and a specificity of 99.3% (95% CI: 96.3-100) for detecting the *CYP2C19*2* allele. Administration of prasugrel to *CYP2C19*2* carriers in the rapid genotyping group significantly reduced the primary endpoint (0%) in comparison with the standard therapy group (30.4%) (p=0.0092). Percentage platelet inhibition was also significantly reduced in *CYP2C19*2* carriers (73.3±20.3% vs. 27.0±13.4%, p<0.0001).
Conclusions: We report the use of the first point-of-care genetic testing device in medicine and demonstrate its feasibility in the clinical setting. Facilitated by point-of-care genetic testing, administration of prasugrel to *CYP2C19*2* carriers following PCI was associated with a significant reduction in high on-treatment platelet reactivity (ClinicalTrials.gov (NCT01184300)).

O-19
Performance of CT coronary angiography in the elderly: does a life time of exposure to cardiac risk factors preclude diagnostic scans?
Gary R Small (Supervisor: Dr. Benjamin Chow)

Background: Coronary artery disease increases with age. Coronary artery calcification however accompanies atherosclerosis and can preclude the accurate assessment of luminal stenosis at CT coronary angiography (CTA). In elderly patients the presence of increased coronary atherosclerosis and accompanying coronary calcification may reduce the ability of CTA to perform diagnostic scans.
Purpose: We sought to determine whether advancing age would be associated with a reduced ability to perform diagnostic CT coronary angiograms
Methods: 2582 patients over the age of 60 years without a prior history of coronary revascularization and in sinus rhythm were identified from a registry of 9060 prospectively enrolled patients attending for a CT coronary angiogram at the Ottawa Heart Institute. Patients were divided into 5 age groups (60-64, 65-69, 70-74, 75-79 and >80 years old). Clinical data was recorded at the time of the CT scan. Coronary artery images were analysed according to a 17 segment model. Non evaluable scans were determined by the presence of >/=5 non evaluable segments.
Results: 45% of patients were male. The median age of patients was 66 years old. The number of non-evaluable studies was 112. Univariable predictors of non diagnostic studies were age, diabetes, peripheral vascular disease, hypertension, serum creatinine, male gender, coronary calcium, the omission of nitro spray prior to imaging, baseline heart rate, metoprolol dose prior to imaging, imaging heart rate, retrospective image acquisition and the number of small coronary arteries (<1.5mm diameter) (p<0.05). On multivariate analysis age was treated as a categorical variable and was a predictor of non evaluable images as were: coronary calcium, male gender, baseline heart rate, imaging heart rate, serum creatinine retrospective image acquisition and the presence of small coronary arteries. The number of non-evaluable scans significantly increased with increasing age (p<0.002) 10% of studies in patients >80 years of age were non evaluable in comparison to 3% in those aged 60-64 years old.
Conclusion: The number of non diagnostic CTA studies increases with age. Cardiac risk factors, technical factors and coronary calcification as well as age contribute to the increasing incidence of non diagnostic studies in the elderly. Despite this 90% of studies performed in patients over 80 years of age were interpretable indicating that CTA remains a useful tool to investigate the elderly despite their life time exposure to cardiac risk factors.

O-20
Postoperative Tracheostomy as an Independent Predictor of Sternal Wound Infection: A Retrospective Study

Louise Sun (Supervisor: Dr. Bernard McDonald)

Purpose: To investigate whether tracheostomy is associated with the development of sternal wound infection (SWI) post cardiac surgery.
Methods: Institutional REB approval was obtained for this retrospective database study. All patients undergoing cardiac surgery via median sternotomy at the University of Ottawa Heart Institute from September 1, 1997 to October 31, 2010 were included. Patients with preoperative tracheostomy in situ and those patients receiving tracheostomy following documented SWI were excluded. The primary exposure was tracheostomy performed during ICU admission. Primary outcome was SWI. Secondary outcomes were in-hospital mortality and ICU length of stay. Perioperative patient characteristics and outcomes were compared between tracheostomy and non-tracheostomy groups. Continuous variables were analyzed using two-sample t-tests and presented as means ± standard deviations. Categorical variables were analyzed using Chi-squared tests and presented as proportions. Statistical significance was defined as $p<0.05$. Variables found to be strongly associated with SWI ($p<0.1$) were entered into a stepwise multifactorial logistic regression model, for the determination of predictors of SWI. Despite not having a significant statistical association with SWI ($p=0.99$), BMI was included the model, as it has repeated been reported to be a predictor of SWI.
Results: Of the 18845 included patients, 411 had tracheostomy performed prior to onset of SWI with a mean time to tracheostomy of 16 days. The incidences of SWI in the tracheostomy and non-tracheostomy groups were 19.53% (80/411) and 0.84% (154/18434), respectively. On univariate analysis, tracheostomy was significantly associated with SWI ($p<0.0001$) and significant increased mortality (30.4% [125/411] vs. 2.6% [472/18434]; $p<0.0001$) and ICU length of stay (44 ± 32.3 days vs. 2.4 ± 3.8 days; $p<0.0001$). On multivariable analysis, tracheostomy was found to be an independent predictor of SWI (OR 2.38, 95% CI [1.60-3.54]). Female gender, BMI, LVEF < 50%, harvesting of internal thoracic arteries, need for dialysis postoperatively, resternotomy, mechanical ventilation >72 hours, reintubation and CARE score were also predictors of SWI.
Conclusion: The 1.2% (234/18845) incidence of SWI in our cohort is in keeping with previously reported rates of SWI following cardiac surgery ranging between 0.4 to 8.6%[1-4]. However, the relationship between tracheostomy and SWI has been variably reported and remains uncertain[1-4]. Rahmanian's multivariable analysis concluded respiratory failure, rather than tracheostomy, was predictive of SWI[3]. Our multivariable model found tracheostomy to be a strong and independent predictor of SWI (OR=2.38), after adjusting for the same surrogates for respiratory failure used in Rahmanian's paper.

O-21
Clinical Impact of Neurocognitive Deficits Following Cardiac Surgery

Hadi Toeg (Supervisor: Dr. Munir Boodhwani)

Objective(s): Neurocognitive deficits (NCDs) have been found to occur frequently following cardiac surgery. Although NCDs have received significant attention in the medical literature and public media, the true clinical impact of these deficits on patient outcomes and quality of life is not well defined.
Methods: Neuropsychometric testing was performed on 696 patients undergoing coronary artery bypass surgery using a battery of 14 tests divided into 4 domains assessing memory, attention, speed, and psychomotor function. Neurocognitive assessments were performed preoperatively (100% complete), at hospital discharge (99% complete), and at 3 months postoperatively (94% complete). Neurocognitive deficits were defined as a drop in scores by 1 standard deviation in ≥ 1 domain. Quality of life was assessed using Short Form 36 and clinical outcomes were recorded. Mean age was 65 ± 8 years and 88% were male.
Results: There was no in-hospital mortality and 99% survived at 3 months. NCDs were identified in 265 (38%) patients at discharge and in 132 (19%) at 3 months. Predictors of NCD at discharge were elevated preoperative creatinine ($p = 0.04$), increased cardiopulmonary bypass time ($p = 0.005$), and diabetes ($p = 0.003$). Intensive care unit stay (1.6 ± 2.2 vs. 1.3 ± 1.3 days, $p = 0.05$) and hospital stay (6.9 ± 4.3 vs. 6.2 ± 2.9 days, $p = 0.01$) were slightly longer in NCD patients. At 3 months, patients experienced improvements in both physical (34 ± 2% increase vs. baseline) and mental (10 ± 1% increase vs. baseline) components of quality of life, independent of the occurrence of NCDs ($p > 0.5$). Independent predictors of quality of life improvement included younger age, severe preoperative symptoms, normal left ventricular function, and absence of post-operative wound infection, but not NCDs (Table 1).
Conclusions: Neurocognitive deficits can be frequently detected on comprehensive neuropsychometric testing following cardiac surgery. However, they are not associated with any clinically important differences in patient outcome or in quality of life after surgery.
Keywords: Quality of life, Neurocognitive deficits, Coronary Artery Bypass Surgery

O-22
The impact of hemodynamic parameters and target-vessel characteristics on hyperplasia of saphenous vein grafts at 1 year: analysis from the CASCADE randomized trial

Dai Une (Supervisor : Dr. Marc Ruel)

Purpose: Areas of intimal hyperplasia in saphenous vein (SV) grafts are linked to subsequent graft atherosclerosis and failure. The CASCADE trial examined whether clopidgrel was protective against SV graft hyperplasia and occlusion, assessed by 1-year angiography supplemented with IVUS. In CASCADE, clopidgrel was not significantly associated with a reduction in SV graft intimal hyperplasia, while consistent statin use was and diabetes constituted a risk factor. Hemodynamic, pharmacologic and anatomical factors were not assessed, and their analysis constitutes the purpose of this study.
Method: We conducted a post-hoc analysis of the CASCADE randomized controlled trial, where 323 grafts were assessed by angiography at 1 year postoperatively. In addition to preoperative demographics and statin use, we added the following factors to multivariate models in order to assess risk factors for SV graft hyperplasia: systolic blood pressure (BP), diastolic BP, mean BP, and resting heart rate at 1 year follow-up, medication profile, stenosis of native target coronary, target vessel location, target vessel quality, target vessel size, and SV diameter.

Results: The mean 1 year SV graft intimal area was 4.31±2.06 mm^2. Univariate analysis indicated that significant predictors associated with SV graft intimal hyperplasia included SV diameter (2.09±0.18 mm^2 per mm diameter; p<0.001), heart rate at follow-up (beats/min) (0.053±0.024 mm^2 per beat/min; p=0.030) and grafting for RCA (1.02±0.44 mm^2; p=0.022). In multivariate linear regression analysis, independent associated predictors were SVG vessel size (2.09±0.18 mm^2; p<0.001) and beta-blocker use (-0.96±0.48 mm^2; p=0.047).
Conclusions: Hemodynamic parameters, graft size and target-vessel characteristic had a strong impact on SV graft hyperplasia at 1 year psotoperatively. Smaller SV grafts, lower heart rate, and use of beta-blockers were protective against SV graft intimal hyperplasia, while blood pressure control was not. Grafting for RCA was a risk factor for SV graft intimal hyperplasia.

O-23
Steroids and the Treatment of Cardiac Sarcoidosis: A Systemic Review

Mouhannad Sadek (Supervisor: Dr. David Birnie)

Purpose: To determine whether patients with cardiac sarcoidosis (CS) benefit from treatment with steroids.
Methods: Studies examining steroid treatment in CS were identified from MEDLINE (1950–2011), EMBASE (1980–2011, week 51), Cochrane Controlled Trials Register (2011), Cochrane Database of Systematic Reviews and National Institutes of Health Clinical Trials.gov database. Two investigators performed abstract screening, paper review and data extraction independently. Inclusion criteria included English publications reporting original outcome data in patients diagnosed with cardiac sarcoidosis (based on the Japanese Ministry of Health and Welfare criteria) and treated with steroids. Exclusion criteria included reports of < 5 subjects and follow-up of < 3 months. Outcomes examined were AV conduction, left-ventricular function, ventricular arrhythmias and mortality.
Results: A total of 1491 references were retrieved. Nine publications reported data on patients with CS treated with steroids and were included in this investigation. There were no randomized trials. In the 9 reports, 240 patients received steroids and 41 patients did not. Prednisone dosing varied between 30-60 mg/day with a variable duration of treatment from 3 to 168 months, and some studies kept patients on maintenance doses. There were 40 patients with AV conduction disease treated with steroids, with 23/40 (57.7%) improving. In contrast 15 patients were not treated with steroids and 0/15 improved. Steroid therapy improved LV function in one study (EF 34.6 +/- 12% to 48.8 +/- 18.6%, p < 0.01), and prevented LV dysfunction in another study compared to no treatment (EF 62.1 +/- 4.4% vs. 37.6 +/- 17.3%, p < 0.005). Short-term mortality appears to be low in steroid treated patients (0% mortality in studies with follow-up 6-7.3 months), while long-term mortality was variable (5-25% 5-year mortality).
Conclusion: Our systematic review found only 9 papers reporting outcomes following steroid therapy. There were no randomized trials. Treatment protocols and outcomes were not standardized and there was a very limited number of non-treated patients. Thus it is not possible to draw conclusions about the utility of steroids in this population. There is a clear need for large multi-center prospective registries in this patient population.

O-24
Recovery of Left Ventricular Systolic Function in New Onset Heart Failure

Michael Chiu (Supervisor: Dr. Lisa Mielniczuk)

Purpose: Rates of incident heart failure (HF) are increasing. Medical and interventional therapy has been shown to improve ventricular function in existing patients, however predictors of recovery and prognosis in new onset patients remain ill defined.
Methods: This study examined 118 patients with newly diagnosed HF (<6 months duration) and ventricular dysfunction, defined as LVEF<40%. The median follow-up time was 25 months (range 4-48 months) with EF normalization defined as EF>40%. Results: A total of 53% of patients had ischemic cardiomyopathy. The mean LVEF at diagnosis was 26% ± 7.8%, and was 37% ± 12% at the end of the study. The mean LVEF improvement was 16%. A total of 74% of patients had LVEF improvement, with normalization observed in 37%. Logistic regression was used to identify predictors of LVEF normalization. The model included six predictors: age, ischemic etiology, previous MI, PVD, ICD requirement, and baseline systolic blood pressure. On multivariate analysis, only previous MI (OR 0.279 95% I 0.083-0.932), PVD (OR 0.163 95% I 0.032-0.823), and ICD requirement (OR 0.283 95% I 0.094-0.850) remained statistically significant. Linear regression was used on the same model to determine if the results were consistent. Similar to the logistic regression, previous MI (p=0.05), PVD (p=0.02), and ICD requirement (p=0.02) remained significant. Logistic regression was also used to predict negative clinical outcomes, which were defined as death, heart transplantation, ICD/CRT insertion, or HF-related hospitalizations. The model consisted of five predictors: ischemic etiology, age, PVD, CAD, and use of a diuretic. Only ischemic etiology (OR 9.312 95% I 1.549-55.976) remained significant.
Conclusions: LVEF improvement is common in patients with new onset HF with normalization of EF observed in 37% of patients over a median study period of 25 months. Patients were less likely to have EF normalization if their heart failure was due to an ischemic cause. Furthermore, these patients were more likely to have negative clinical outcomes such as death, hospitalization, or ICD/CRT implantation.

ALLIED AND POPULATION HEALTH ORAL PRESENTATIONS

O-25
Triaging Patients for Exercise Stress Testing in Cardiac Rehabilitation

Jennifer Harris (Supervisor: Dr. Pipe)

Background and Aims: It is typical for cardiac rehabilitation (CR) programs to use a graded exercise stress test (GXT) for risk stratification and exercise prescription. Current CACR guidelines stipulate that all patients should complete a symptom-limited GXT. There is a lack of evidence supporting mandatory GXT for all CR patients. A 2005 internal review at the University of Ottawa Heart Institute (UOHI) revealed that stress testing all patients was a barrier to accessing CR. In 2005 patients were waiting 90 days for an intake GXT. A mandatory GXT prior to CR participation was subsequently eliminated to decrease wait

times. A triage algorithm was developed to assess the need for a GXT to ensure that that a consistent approach was applied to all patients and that individual patient needs were met. Initial criteria for the conduct of a GXT included: the level of supervision by CR staff; patient intentions to exercise vigorously; the presence of cardiac symptoms; an out-of-hospital cardiac arrest; a history of palpitations; or, the presence of an AICD. Ongoing assessment could result in a patient being referred for a GXT after their CR program commences.
Methods: All patients entering the UOHI CR program undergo a thorough assessment by physiotherapists and nurses. The algorithm is used to determine the need for a GXT. A review of our experience in applying the algorithm was undertaken from January 2011 to April 2011.
Results: 498 patients enrolled in CR in the interval noted. 154 (31%) had a GXT ordered at CR program intake. Of these 144, 89% of them were male. Of further note 52% were entering moderate and high intensity onsite exercise programs and 48% were entering a home program option. None of the patients were entering low intensity (LI) onsite programs. All of the onsite LI patients undergo a 6 min walk test. The most common reasons for ordering a GXT included chest pain and an intention to participate in vigorous exercise programs. Prior to the introduction of this new approach, the average wait time before enrollment in CR was 12 weeks; it is now less than 3 weeks.
Conclusions: The implementation of an algorithm to better triage patients to receive a GXT has, among other factors, improved access to care by decreasing wait times and significantly reducing the burden of exercise testing. Further research is needed to provide evidence based recommendations for exercise stress testing in CR patients.

O-26
A comparison of cardiovascular risk between Chinese and South Asian Canadians, and residents in China and India: a pilot investigation.

Eftyhia Helis (Supervisor: Dr. J. George Fodor)

Purpose: Studies in Canada have shown that individuals of Chinese or South Asian descent may be at increased risk for developing heart disease and stroke compared to Caucasians. We were interested in studying whether the different cardiovascular disease (CVD) patterns observed among these ethnic groups in Canada are simply reflecting the trends already present in their countries of origin or they change as a result of exposure to the Canadian/Western lifestyle. We designed a pilot study to test the feasibility of collecting and comparing CVD risk data of South Asian and Chinese respondents residing in Canada and respondents in India and China.
Methods: This international, observational pilot study was conducted among employees of the *Ottawa Hospital (Civic Campus and UOHI Campus in Ottawa), Fu Wai Hospital in Beijing (China), Medwin Hospital in Hyderabad (India)* and the *Taj Mahal Palace hotel in Mumbai (India).* A CVD risk assessment chart (Gaziano TA., Lancet 2008) was used to predict the 5-year CVD risk score of respondents. Gender, age, diabetes, smoking, systolic blood pressure and body mass index were evaluated and an assessment was performed for each respondent in approximately 30 minutes. The study was centrally coordinated by the UOHI and the local research teams in China and India received training for the implementation of the study using an identical protocol. This research was approved by the institutional research ethics bodies in Ottawa, Beijing, Hyderabad and Mumbai.
Results: Three hundred and thirty five eligible respondents enrolled in the study. In Mumbai, the screening identified 41% of employees who were at moderate or high risk for developing CVD in the next five years. For each of the Ottawa, Beijing and Hyderabad samples, the corresponding rates for elevated CVD risk were 3%, 11% and 9% respectively. The prevalence of hypertension (45%), smoking (24%) and diabetes (16%) were the highest among the employees of the Taj Mahal hotel. The response rate at the Ottawa site was much smaller than anticipated (33%).
Conclusion: This pilot study established a collaboration of research teams in Canada, China and India and demonstrated the feasibility of using a non-laboratory assessment tool for a quick and inexpensive identification of high CVD risk individuals at their workplace. The gathered information and "lessons learned" from this study will inform the design of future larger - scale studies of CVD risk in these populations in Canada, China and India so that the their specific CVD needs may be addressed appropriately.

O-27
A case-managed home program for primary and secondary prevention of cardiovascular disease: Clinical results of the *FrancoForme* Program.

Marc Laflamme (Supervisor: Dr. Michele de Margerie)

Francophones in Ontario are at higher risk of cardiovascular disease when compared to their Anglophone counterparts, according to the *Second Report on the Health of the Francophones in Ontario* (2005). The ***FrancoForme*** Program, receiving base funding from the Champlain LHIN, was designed to reduce cardiovascular risk factors through weekly lifestyle interventions by telephone contacts over a 3-month period. The program accepts participants for primary prevention if they are Franco-Ontarian with one or more risk factors for heart disease, as well as Francophones with documented heart disease.
Methods: We recruited 769 participants from the Champlain Region through referrals from family physicians offices, the Eastern Ontario Health Unit and from the University of Ottawa Heart Institute. At Intake, 3-month, and 1-year time points, all participants had their weight, height. fasting glucose, lipid profile, blood pressure and weekly minutes of exercise recorded and completed a questionnaire assessing individual sense of well-being. Interventions consisted of an initial on-site visit with a Physiotherapist or Nurse-mentor, followed by weekly telephone interventions directed at educating and motivating the participant specifically in the areas of exercise, nutrition, smoking cessation and stress management, as applicable. These interventions lasted 20 minutes on average and were ongoing for 3 months. Also, appropriate educational material was provided to each participant.
Results: Out of 769 who started the program, 491 completed the program and 166 completed a 1-year follow-up assessment. Those who did not complete the 3-month follow-up were not contacted at the 1-year time point. The mean age was 63.1 +/- 11.4 years and M/F ratio was 51/49. Only 10% of participants smoked at baseline; this fell to 7.5% at 3 months and 5.4% at 1 year. Paired *t*-tests showed

significant improvements in most modifiable risk factors at the 3-month follow-up time point. Among participants with baseline SBP value ≥ 140 mmHg, the mean SBP decreased by 15 mmHg (p=0.001). In participants with TC ≥5.17 mmol/L, TC decreased by 0.7 mmol/L (p=0.001); LDL-C ≥3.36 mmol/L was reduced by 0.8 mmol/L (p=0.001); HDL ≤ 1.03 mmol/L increased by 0.1 mmol/L (p=0.001); triglycerides ≥ 1.69 mol/L decreased by 0.4 mmol/L (p=0.001). Baseline blood glucose ≥ 5.6 mmol/L decreased by 0.2 mmol/L (ns). Exercise less than 90 min/week increased to 152 min/week (p=0.001). For obese participants (BMI ≥30), mean weight decreased by 1.7 kg (p=0.001). Self reported physical and mental health status also improved significantly (p=0.001). These significant changes were maintained after 1 year.
Conclusion: Personalized intervention in a group of Francophones in Eastern Ontario has a significant impact on reducing cardiovascular risk factors through lifestyle modification. This approach is practical, inexpensive and is easily accessible for participants from both rural and urban communities.

O-28
Randomized trial of an interactive, voice response-mediated follow-up system for smoking cessation in smokers with coronary heart disease

Kerri-Anne Mullen (Supervisor: Dr. Robert Reid)

Background: Smokers with coronary heart disease (CHD) benefit from cessation counseling in hospital if it continues after discharge. A randomized controlled trial was conducted to determine if continuous abstinence from smoking would be higher 26 and 52 weeks after discharge in smokers who received interactive voice-response (IVR) mediated telephone follow-up and triage to nurse counseling compared to those receiving standard care.
Methods: A total of 440 smokers (≥ 5 cigarettes/d) hospitalized with CHD were randomized to either standard care or IVR. Standard care included: in-hospital nurse counseling; nicotine replacement therapy (NRT) during hospitalization; and a recommendation for ongoing NRT following discharge. Participants in the IVR group received standard care and also received automated telephone calls 3, 14, 30, 60, 90, 120, 150 and 180 days after discharge. During the call, the system posed a series of questions concerning smoking status, confidence in staying smoke-free, and use of cessation medications. If the patient identified that they had resumed smoking or indicated that their confidence in remaining smoke-free was low, they were contacted by a nurse-counselor who provided additional assistance. The primary outcome was confirmed continuous abstinence for weeks 1-26 after hospital discharge.
Results: The continuous abstinence rate, adjusted for potential misreporting, was significantly higher in the IVR compared to the standard group for weeks 1-26 (38.7% vs. 29.5%; OR = 1.58; 95% CI: 1.04-2.42; P = 0.034). Continuous abstinence for weeks 27-52 was clinically but not statistically higher in the IVR group (35.6% vs. 28.6%; OR = 1.45; 95% CI: 0.94-2.22); P = 0.093).
Conclusions: IVR-mediated triage to nurse counseling lead to a statistically significant increase in abstinence 26 weeks after discharge among smokers with CHD. The benefit of IVR was not statistically significant at 52 weeks, although there was a positive trend. IVR is a promising means of directing limited hospital resources to smokers in need of ongoing support after discharge.

O-29
A Social Ecological Approach to Understanding Physical Activity: A mixed methods exploration of the individual, family and neighbourhood characteristics that influence physical activity among Family Heart Health: Randomized, Controlled Trial participants

Dana Riley (Supervisor: Dr. Robert Reid)

The purpose of this thesis was to better understand physical activity (PA) behaviour change among family members of people with coronary heart disease (CHD) who participated in a randomized controlled trial of a behavioural risk reduction intervention. Using a social ecological approach, a three-part research program was employed to examine the relationship between PA outcomes and factors at the individual, family and neighbourhood levels, respectively.
Study 1 – Individual: The purpose of this study was to determine whether a 12-week behavioural risk reduction intervention caused self-reported moderate-vigorous PA (MVPA) to increase and to identify the associated Theory of Planned Behaviour (TPB) constructs. Three hundred twenty-four physically inactive (<150 minutes/week MVPA) participants were enrolled in a randomized controlled trial. The main outcome was achievement of guideline recommended levels of MVPA (≥150 minutes/week) at 12-weeks. Groups were compared using logistic regression. TPB constructs were examined using t-tests and Spearman rank correlations. Intervention participants were significantly more likely to meet MVPA guidelines at 12-weeks (OR=3.54, 95% CI 2.22-5.63, p<.001). The outcome was significantly correlated with increases in control belief, behavioural belief, subjective norm, attitude, perceived behavioural control and intention (all p<.01) among intervention participants and attitude (p<.01) and intention (p<.01) among controls.
Study 2 – Family: Semi-structured interviews were conducted with 36 participants to elicit perceptions of the factors in the social and physical environment that influence PA. Interviews were audiotaped, transcribed, coded and analyzed, which involved inductively documenting emerging themes. Spouses were more likely to provide care and support and to engage in PA with their spouse after the CHD event. Many spouses expressed that their own PA was limited by the capabilities of their partner. Offspring expressed an increased perception of their own future risk of CHD, citing genetics as a prominent concern; however, this did not necessarily translate into PA behaviour change. The data suggests awareness of an increased susceptibility to CHD is not stimulating participants to increase their own PA to prevent future risk, particularly among offspring, but they may take other actions. Spouses are more likely to engage in PA with the CHD patient than offspring, suggesting this shared social environment can promote PA, although intensity may be limited. Family members may need additional interventions to translate their perceived future risk of CHD into current PA behaviour change.
Study 3 – Neighbourhood: Self-reported PA from a prospective behavioural risk reduction intervention was explored in the context of objectively measured Walk Scores and neighbourhood walkability in Ottawa, Canada. Participants in the intervention arm had significantly higher odds of meeting PA guidelines at 12-weeks compared to the standard care control group. This was not influenced by Walk Scores or walkability. This individual-level intervention was effective in assisting participants to overcome potential structural barriers presented by their neighbourhood to meet PA guidelines at 12-weeks.

Conclusion: This thesis provides novel insights into the relationships between PA and factors at the individual, family and neighbourhood levels in a sample of family members of patients with CHD. Specifically, the FHH-RCT intervention was effective for increasing self-reported moderate-vigorous PA, regardless of Walk Score or neighbourhood walkability. To gain even greater health benefits, family members may need additional information or intervention in order to translate their perceived future risk of CHD into current PA behaviour change.

O-30
Impact of Acute Versus Stable Coronary Heart Disease on Smoking Cessation Success

Ashley Armstrong (Supervisor: Dr. Robert Reid)

Purpose: Smoking cessation has been established as the leading secondary prevention intervention for patients with coronary heart disease (CHD). Hospitalization for CHD is said to result in an increased motivation to quit smoking. The objective of the current analysis was to determine the impact of admitting diagnosis on quit rates one year post hospital discharge.
Methods A secondary analysis was conducted using data assembled from a randomized control trial of smokers with CHD. From July 2006 to October 2009, smokers (> 5 cigarettes/day) admitted to the University of Ottawa Heart Institute for acute coronary syndrome (ACS), elective percutaneous coronary intervention (PCI), diagnostic catherization or elective coronary artery bypass graft (CABG) received in-hospital pharmacotherapy and counseling for smoking cessation. The primary outcome of interest was validated abstinence from smoking – expired carbon monoxide (CO) – at 52 weeks post hospital discharge. A logistic regression was performed to assess the impact of diagnosis on the primary outcome while controlling for age, gender and nicotine dependence at baseline.
Results: Four-hundred and one patients were included in the outcome analysis. Three quarters of the sample were male (74.6%) with a mean age of 54 ± 9 years. The CO verified quit rates at 52 weeks post hospital discharge for patients admitted for ACS, CABG, diagnostic catherization and elective PCI were 31.5%, 16.0%, 15.3% and 13.3% respectively. Individuals with ACS were found to be 2.81 times more likely to quit smoking than those with CABG, PCI or CATH, $p<.001$
Conclusions: The acuity of the admitting diagnosis had a significant effect on quitting success in smokers with CHD. Quit rates were the highest for those experiencing an acute event; rates were substantially lower for patients admitted for elective investigational or revascularization procedures. Additional cessation assistance and relapse prevention strategies may be required in those with more stable or longer duration disease.

BASIC SCIENCE POSTER PRESENTATIONS

P-1
A Collagen Matrix Scaffold for Endothelial Progenitor Cell Therapy Improves Myocardial Viability, Perfusion, and Function through Enhanced Cell Retention and ILK Expression in a Mouse MI Model

Ali Ahmadi (Supervisors: Dr. Erik Suuronen and Dr. Marc Ruel)

Background: To improve cell therapy, we tested echo-guided intramyocardial delivery of endothelial progenitor cells (EPCs), with and without a collagen matrix, in a mouse model of myocardial infarction (MI). We studied the potential role of the matrix in enhancing cell retention, as well as myocardial perfusion, viability, and function. As integrin-linked kinase (ILK) is involved in cell survival and has been shown to be upregulated in hypoxic EPCs upon adhesion to a collagen substrate, we also investigated the effect of collagen matrix on ILK expression in infarcted hearts.
Methods: Seven days after left anterior descending coronary artery ligation, C57BL6/J female mice were randomly allocated to receive one of the four following treatments: EPCs (n=29), collagen matrix alone (n=19), EPC+collagen matrix (n=29), or PBS (n=15). EPCs were green fluorescent protein $(GFP)^+$ marrow derived cells from C57BL/6-Tg(CAG-EGFP)1Osb/J male mice. ^{13}N-ammonia and ^{18}F-FDG PET imaging (on randomly selected mice), as well as echocardiography (on all mice), were performed at the time of treatment (baseline) and 3 weeks later (follow-up). Hearts were collected for immunohistochemistry (for examination of transplanted cell retention, LV mass preservation, and arteriole density) and Western Blot (ILK expression) analysis.
Results: Follow-up ejection fraction (EF) was at least 1.4-fold greater in the EPC+matrix group (EF=56±2%) compared to all other groups (≤40±2%; $p<0.001$). Fractional shortening was also 1.5-fold higher in EPC+matrix group (42.6±2.3% versus ≤27.0±2.1%; $p\leq0.001$). PET analysis showed improved viability and perfusion (by 35% and 29%, respectively; $p\leq0.05$) only after treatment with EPC+matrix. Histology showed an anterior to posterior LV wall thickness ratio of 0.7±0.1 in EPC+matrix group, which was significantly greater than for all other groups (≤0.3±0.0; $p<0.001$). More arterioles were detected in hearts injected with EPC+matrix (10.9±1.1 per field of view) compared to the other treatments (≤6.2±0.5; $p<0.001$). Moreover, detection of the Y chromosome by Q-PCR indicated greater intramyocardial retention of transplanted cells in EPC+matrix group (by 7.1±0.5-fold) relative to the EPCs-only group ($p=0.003$). ILK expression was higher in hearts treated with EPC+matrix (1.4±0.1 fold) or matrix (1.6±0.1 fold) compared to hearts treated with EPCs-only or PBS ($p\leq0.02$).
Conclusions: The collagen matrix enhanced transplanted cell retention and promoted greater vascular density. Also, the combined EPC+collagen matrix therapy preserved LV wall mass, and enhanced myocardial perfusion and viability, potentially via the ILK pathway. We have demonstrated promise for the use of collagen-based matrices for enhancing the benefits of cardiac cell therapy.

P-2
Evaluation of ^{18}F-HFB labeled collagen matrix after intramyocardial injection in a mouse MI model

Ali Ahmadi (Supervisors: Dr. Erik Suuronen and Dr. Marc Ruel)

Background: Injectable matrices have been shown to improve the regenerative effects of endogenous and exogenous progenitor cells by enhancing their recruitment, retention and survival within ischemic tissues *in vivo*. However, the thermogelling and retention properties of injectable scaffolds after delivery to a contractile tissue are yet to be investigated. Our objective was to show that a hexadedecyl-4-[^{18}F]fluorobenzoate (^{18}F-HFB) tracer can effectively label a collagen

matrix and be used to evaluate matrix retention upon ultrasound-guided myocardial injection into infarcted mouse myocardium.
Methods: Ice cold glutaraldehyde cross-linked rat tail collagen type 1 matrix was labeled with ^{18}F-HFB tracer and incubated at 37ºC for 30 minutes. After rinsing with phosphate buffer saline, the gel radioactivity was measured. The *in vivo* retention of ^{18}F-HFB labeled collagen matrix at the site of injection was validated by PET scans: 7-14 days after ligation of LAD in 9-10 week old C57BL6/J female mice, the animals were injected with ^{18}F-NaF (7.5±1.4 MBq) to demarcate the skeleton and with ^{13}N-NH3 (42.5±4.8 MBq) to delineate the infarcted myocardium during a single scan.^{18}F-HFB (3.1±0.9 MBq) labeled matrix was injected to infarct and peri-infarct areas and scans were performed 10 minutes and 2 hours later. Co-registration of images was conducted by merging the demarcated skeleton. Finally the mice were sacrificed and different tissues were collected for biodistribution assessment using a gamma counter.
Results: *In vitro*, the ^{18}F-HFB labeled matrix retained the radioactive tracer immediately after solidification with a ratio of 82±1% (n=12). The tracer retention ratios after 2 and 4 hours were 82±1% and 83±1%, respectively (n=12). For *in vivo* analysis, signal intensity quantification was performed using Inveon Research Workplace software and showed that the activity detected 2 hours after injection was 95±5% of the initial activity detected at 10 minutes post-injection. Biodistribution analysis of different organ radioactivity indicated a significantly higher activity in the myocardium compared to all other tissues (38±13% of injected dose/gram of tissue; n=10, $p<0.05$).
Conclusions: This study demonstrates that a glutaraldehyde cross-linked collagen matrix injected into the infarcted heart solidifies at body temperature quickly enough to be retained in the contractile myocardium. This also confirms the accuracy of ultrasound-guided myocardial injections for treatment delivery.

P-3
Serum interferon alpha-21 is a biomarker that predicts coronary artery disease in individuals homozygous for the 9p21.3 risk locus.

Naif A.M. Almontashiri (Supervisor: Dr. Alexandre F.R. Stewart)

Background and Purpose: The 9p21.3 locus confers risk for coronary artery disease (CAD) by an unknown mechanism. Enhancers at the 9p21.3 locus remodel chromatin at *CDKN2B*, *CDKN2A*, *MTAP* and between the interferon alpha-1 (*IFNW1*) and interferon alpha-21 (*IFNA21*) genes. Here, we tested whether protein expression from these genes correlates with the 9p21.3 risk genotype.
Methods and Results: Using immunoblot analysis of protein extracts from primary cultures of human aortic smooth muscle cells (n=6) and peripheral blood mononuclear cells from patients with CAD (n=18) genotyped for the 9p21.3 risk locus using SNP microarrays, we found that p16 (from the CDKN2A gene) expression in both cell types, and p15 (from CDKN2B) expression in aortic smooth muscle cells was negatively associated with 9p21.3 risk genotype. No association between MTAP expression and 9p21.3 genotype was seen. However, a strong positive correlation ($p<10^{-4}$) between IFNA21 levels and 9p21.3 risk genotype was seen in both cell types. ELISA analysis of serum from 231 angiographically normal individuals and 331 CAD patients showed highly elevated levels of IFNA21 in individuals homozygous for the 9p21.3 risk allele ($p=2.7x10^{-89}$). ELISA of serum IFNW1 and IFNA4 showed that the 9p21.3 effect is specific to IFNA21. Importantly, elevated serum IFNA21 levels were 3 times higher in homozygous carriers of the 9p21.3 risk genotype with CAD than without (odds ratio per 100 pg/ml increase 3.27, $p=8.8x10^{-11}$).
Conclusions: Elevated serum IFNA21 is a biomarker that predicts coronary artery disease with homozygosity for the 9p21.3 CAD risk locus. Since 25% of the population with European ancestry is homozygous for this locus, IFNA21 is a powerful new diagnostic tool to detect CAD without the need for angiography. Together with reduced p16 expression, elevated IFNA21 may contribute for the risk of CAD associated with the 9p21.3 locus.

P-4
In vitro Cell-Material Interactions of Physically Cross-Linked Chitosan Derived Hydrogels for Tissue Engineered Scaffold Applications

Anna Badner (Supervisor: Dr. Erik Suuronen)

Purpose: Injectable hydrogels are becoming increasingly attractive for cell therapy applications. Physical cross-linking of the polymer hydrogels (as opposed to traditional chemical cross-linking) has the potential for reduced toxicity and consequently greater therapeutic potential in cell therapy. Cell-material interactions (viability, adhesion and migration) were assessed in two physically cross-linked chitosan-derived hydrogels for their potential use as scaffolds in tissue engineering.
Methods: The biocompatibility of two physically cross-linked chitosan-derived hydrogels was assessed: (a) chitosan derivative N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) ionically cross-linked by sodium tripolyphosphate (TPP); and (b) pure chitosan hydrogels obtained via ionic cross-linking with β-glycerolphosphate disodium salt (β-GP). Human blood-derived circulating progenitor cells (CPCs), human umbilical vein endothelial cells (HUVECs) and porcine islet cells were applied for cell-material interaction studies. The adhesion and viability was assessed on days 1, 2 and 5 using 4',6-diamidino-2-phenylindole (DAPI) stain and live/dead viability assays, respectively. CPCs and HUVECs migration through and towards the hydrogel biomaterials was also studied on days 3, 5 and 7 using a Boyden chamber with VEGF as chemo-attractant.
Results: Both physically cross-linked chitosan-derivative hydrogels were found to be non-toxic to CPCs, HUVECs and islets (n=6). The β-GP hydrogel supported greater adhesion and viability throughout the 5 day study when compared to the HTCC-TPP material. Cell migration of CPCs towards β-GP material was greater than that of a comparable fibronectin control after 3 (p=0.003) and 5 (p=0.013) days. There was no difference between CPCs and HUVECs migration towards HTCC-TPP and the control.
Conclusion: The β-GP hydrogel displays favorable cell-material interactions and holds promise as a tissue-engineered scaffold for cell therapy.

P-5
Mitochondrial Plasticity Alters Calcium Handling in Differentiated C_2C_{12} Myotubes

Bou Khalil, Maroun (Supervisor: Dr. Calum Redpath)

Purpose: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The high frequency electrical activity in the fibrillating human atrium *in vivo* is associated *in vitro* with electrophysiological remodeling, calcium overload and apoptotic cell death. In surviving myocytes aberrant calcium handling promotes re-initiation or perpetuation of AF. Privileged inter-organelle calcium signaling has recently been shown to occur in cardiac myocytes via the mitochondria-associated membrane, the physical association of juxtaposed sarcoplasmic reticulum (SR) and mitochondrial membranes. Moreover, calcium overload alters mitochondrial plasticity, raising the possibility that the mitochondrial membrane may represent a focal point for arrhythmogenesis.
Methods: We investigated the relationship between mitochondrial plasticity and calcium signaling using the C_2C_{12} mouse myoblast cell line. Myoblasts were induced to form contractile myotubes using low-serum differentiation medium for 96 h at 37°C in an atmosphere of 10% CO_2. C_2C_{12} cells were infected (500 MOI) with dominant-negative dynamin-related protein 1 ($DRP1_{K38E}$), a mutant form of the mitochondrial fission factor that promotes an elongated mitochondrial reticulum when expressed in cells. Laser scanning confocal imaging was then used to monitor spontaneous calcium sparks and release in control and $Drp1_{K38E}$-infected C_2C_{12} myotubes. Subsequently, calcium release from intracellular stores was studied by fluo-4 video microscopy after administration of caffeine (4 mM).
Results: Under control conditions, no spontaneous fluorescence was observed. Enhanced expression of the fission factor Drp1 was confirmed in C_2C_{12} myotubes using immunoblotting, with Drp1 translocation to the mitochondrial membrane observed by confocal microscopy. Forced expression of the dominant-negative $Drp1_{K38E}$ mutant protein resulted in elongated mitochondrial reticula in C_2C_{12} cells. Altered mitochondrial plasticity was associated with a 2.5-fold increase in SR calcium release in $Drp1_{K38E}$-infected cells (control 860 ± 402 cf. $Drp1_{K38E}$ 2181 ± 433 fluorescence arbitrary units, n=40, $p < 0.00001$, *Student's t-test*). Expression of $Drp1_{K38E}$ also resulted in slower decay of the fluorescence (t50, control 88 ± 4 cf. $Drp1_{K38E}$ 99 ± 5 seconds; t90, control 89 ± 3 cf. $Drp1_{K38E}$ 204 ± 3 seconds; n=40, $p < 0.00001$, *Student's t-test)*. The spatial pattern of calcium signals was invariably synchronous and homogeneous throughout the myotubes in both groups.
Conclusions: Our results reveal, for the first time, that altered mitochondrial plasticity results in changes in SR calcium release and calcium reuptake in cultured myotubes. Further work to elucidate the mechanisms of this altered calcium handling and the ensuing physiological implications in cardiomyocte models are ongoing.

P-6
Gli2 enhances cardiomyogenesis in mouse embryonic stem cells by recruiting Brg1 to the cardiac progenitor gene, *Mef2c*

Joel Fair (Dr. Ilona Skerjanc)

Purpose: Following myocardial infarction, approximately one billion cells need to be replenished to re-establish proper heart function. Embryonic stem (ES) cells are a promising tool for myocardial repair due to their plasticity and ability to self-renew. However, efficient differentiation of ES cells into cardiomyocytes is required before effective, clinical application. Recently, protocols have been established to enhance differentiation of mouse ES cells (mES) and human ES (hES) cells into cardiomyocytes. While it is known that Gli2 induces cardiomyogenesis in P19 embryonal carcinoma (EC) cells, a well-established model of embryonic stem cells, we set out to determine the role of Gli2 in mES cells.
Methods: We created mES cells with stable overexpression of Gli2 and examined the effects of Gli2 overexpression on the induction of mesoderm, cardiac progenitors and mature cardiomyocytes by quantitative polymerase chain reaction (qPCR) analysis of marker gene expression. Immunofluorescence of the contractile protein MyHC was used to determine the overall effects of Gli2 overexpression on cardiomyogenesis. Mass spectrometric analysis of proteins co-immunoprecipitating with Gli2 was used to identify Brg1, a novel Gli2-interacting protein that may facilitate the enhancement of cardiomyogenesis by Gli2. Chromatin-immunoprecipitation (ChIP) using antibodies against Gli2 or Brg1 examined the association of these proteins to the Gli2-target gene, *Mef2c*, in P19 EC cells with and without exogenous Gli2.
Results: Analysis of cardiac progenitor transcripts in mES cells by qPCR showed a significant increase in the transcript levels of cardiac progenitor genes, *Nkx2-5, Mef2c and Tbx5,* when Gli2 was overexpressed. However, transcripts of the mesoderm markers Brachyury T and Mesp1 were not significantly affected. Cardiac-specific MyHC transcript levels were significantly up-regulated and there was an increase in MyHC-positive cells by immunofluorescence. Together, these results indicated that Gli2 enhances cardiomyogenesis at the cardiac progenitor stage in mES cells. Co-immunoprecipitation and mass spectrometric analysis revealed that Gli2 and Brg1 could be found in a protein complex. Preliminary results of Brg1- and Gli2-ChIP in P19 EC cells with and without exogenous Gli2 indicated that Gli2 recruits Brg1 to the first intronic region of the *Mef2c* gene.
Conclusions: This study shows that Gli2 enhances cardiomyogenesis through up-regulation of cardiac progenitor genes in mES cells. Gli2 is capable of recruiting Brg1 to a regulatory region of the cardiac progenitor gene, *Mef2c*. This mechanism suggests that Gli2 enhances cardiomyogenesis by recruiting the Brg1/Brm-associated factor (BAF) and its chromatin remodelling features to the regulatory regions of cardiac progenitor genes.

P-7
Effect of Phorbol-12-Myristate-13-Acetate Treatment on Migration of Human Circulating Angiogenic Cells

Khrystyna Herasym (Supervisor: Dr. Erik Suuronen)

Purpose: Stem cell and tissue engineering therapy represent a promising area of research for accelerating adult neovascularization and damaged tissue repair. Many studies have shown a link between the serine/threonine Protein Kinase C (PKC) family and endothelial cell (EC) or endothelial progenitor cell (EPC) proliferation and homing. Because some PKC isoforms are targets of 4-β phorbol esters, the goal of this project was to investigate if Phorbol-12-Myristate-13-Acetate (PMA) could enhance the migratory potential, viability and endothelial-like phenotype of circulating angiogenic cells (CAC) in a PKC-dependent manner.
Methods: The mononuclear fraction was collected from peripheral blood of healthy donors. After 4 days of culture on fibronectin in endothelial basal medium, the adherent cells were considered to be CACs. Transwell microporous inserts placed on top of 12-well plates

were used in order to evaluate the migratory potential of CAC after a 24h exposure to a vascular endothelial growth factor (VEGF) gradient (50ng/mL). CACs that migrated were stained with DAPI and counted from 6 different microscopic fields. Cell viability was assessed by Vi-Cell XR Cell Viability Analyzer. For some experiments, PKC inhibitors were used: Gö6976 (isoform α-specific) and GF 109203X-HCl (non-specific). The expression of PKC and endothelial surface markers such as CXCR4 and CD31 was analyzed by Western blotting.
Results: The optimal PMA concentration to trigger CAC migration was determined to be 1nM compared to other PMA concentrations ($p \leq 0.005$, n=3). It was possible to use inhibitory concentrations of 1uM for Gö6976 (IC_{50}=2.3nM) and 4uM for GF 109203X (IC_{50}=2uM), without decreasing cell viability. However, simultaneous treatment of CAC with PMA and Gö6976 or GF 109203X did not decrease the PMA-induced migration. The effect of 4-α PMA (inactive isomer) was comparable to control. There was no difference in the CXCR4 and CD31 expression between 4-β PMA, 4-α PMA and control treatment.
Conclusions: PMA treatment (1nM) significantly increased CAC migration, stereospecifically with respect to 4-β PMA. Whether this process is PKC-dependent still remains unclear.

P-8
A novel cardioprotective role of ZFP260 transcription factor against Doxorubicin-induced cardiotoxicity
Hiba Komati (Supervisor: Dr. Mona Nemer)

Background and Purpose: Doxorubicin is among the most potent chemotherapeutic agents used for the treatment of a wide variety of tumors; however, its usefulness is limited due to its cardiotoxicity associated with cytoplasmic vacuolization, myofibrillar disorganization and myocyte apoptosis. Doxorubicin induced-cardiotoxicity is a serious clinical problem as it leads to myocyte loss and irreversible cardiomyopathy. We previously showed that low dose infusion of the alpha1-adrenergic agonist Phenylephrine (PE) protected against doxorubixin induced heart failure. More recently, we identified a novel cardiac transcription factor, phenylephrine-induced complex-1 (PEX1) also known as ZFP260, as a mediator of alpha1-adrenergic signaling and an inducer of the adaptive hypertrophic response of the heart. In this work we aimed to assess the potential cardioprotective role of PEX1 transcription factor through gain- and loss-of-function studies.
Methods and Results: To address the protective role of PEX1 transcription factor in vivo, transgenic mice lines with inducible and cardiac-specific overexpression of PEX1 were treated with a single i.p. injection of Doxorubicin at a dosage of 15 mg/kg body weight. After one week, two-dimensional guided M-mode echocardiography (Vevo® 2100 System) was performed on these mice under conscious sedation. Importantly, transgenic mice showed significantly improved cardiac function and reduced apoptotic nuclei comparing to control mice. Using cultured primary cardiac myocytes, we confirmed the direct cardioprotective role of PEX1. Interestingly, overexpression of PEX1 significantly attenuates Doxorubicin-induced myocyte apoptosis as evidenced by the absence of TUNEL-positive nuclei. In contrast, downregulation of PEX1 expression in cardiomyocytes showed decreased survival in the absence of treatment and an exaggerated response to Doxorubicin-induced apoptosis. We found that the mechanisms underlying the cardioprotective effects of PEX1 involve mitochondrial dependent apoptosis via upregulation of the anti-apoptotic genes Bcl2 and BclXL and downregulation of pro-apoptotic genes BAX and PUMA.
Conclusion: The work revealed an essential role of PEX1 in myocyte survival against drug-induced cardiotoxicity. Identification of the transcriptional networks that regulate cardiomyocyte survival and adaptive stress response of the heart could lead to exciting new avenues for cardioprotection and prevention of end-stage heart failure.

P-9
Regenerative Effects of a Collagen Matrix Are Amplified in Necrotic and Dystrophic Microenvironments
Drew Kuraitis (Supervisor: Dr. Erik Suuronen)

Purpose: Previous studies have shown that an injectable, collagen-based matrix can activate endogenous progenitors and stimulate regeneration of ischemic muscle. This study sought to characterize the potential of this regenerative therapy in other myopathies and to describe the role of necrotic environments in matrix-augmented regeneration.
Methods: The EDL muscle, used to monitor disease progression, was injected with PBS or collagen matrix, in two animal models: mdx mice, whose muscles experience constant necrosis; and MLC/SOD mice, which experience constant, non-inflammatory atrophy. Muscle function and phenotype were assessed using a treadmill and qPCR. Muscle progenitor satellite cell (SC) cultures were obtained from wildtype C57 mice and cultured under standard conditions or on the matrix, also ± the addition of necrotic myocyte debris (NMD), prepared from dead myocytes. After 24h in differentiation medium, myotubes were assessed morphologically and with qPCR. SC conditioned medium (CM) was collected and applied to C2C12 myoblast cultures and also screened using cytokine arrays.
Results: Matrix treatment allowed mdx mice to run 41% further and at speeds 22% faster than PBS treatment ($p \leq 0.02$), and also displayed increases in myogenic transcripts pax3 (5.9×), myogenin (3.0×), desmin (2.3×) and myf5 (3.5×; all $p \leq 0.4$). There were no differences in the running abilities between treated MLC/SOD animals ($p \geq 0.7$) or between any myogenic transcripts ($p \geq 0.3$). After 24h in culture, there were 3.3× more myotubes on matrix cultures ($p < 0.05$) and some were seen to spontaneously beat, something that does not typically occur until after 48-72h in culture. Matrix-NMD stimuli generated the thickest and longest myotubes (by 38 & 149%, respectively; $p < 0.05$). Matrix culture increased gene expression of mef2c, myoD and myogenin (up to 50%; $p < 0.05$), but matrix-NMD stimuli greatly increased the expression of these markers (up to 1210%; $p < 0.05$). When CM was added to myoblast cultures, CM from matrix-NMD cultures increased transcription of mef2c (7.1×) and myogenin (3.2×; all $p \leq 0.02$) in C2C12 cells at 24h compared to all other CM treatments. These differences were abrogated by 48h. Interleukin-4, interleukin-6, hepatocyte growth factor and stromal cell-derived factor-1 were increased only in matrix-NMD conditions (by 1.4×, 3.0×, 1.8×, 1.4×, respectively; all $p < 0.05$).
Conclusions: The in vivo and in vitro observations suggest that myogenesis induced by treatment with a collagen matrix is greatly amplified in necrotic environments. Furthermore, interaction of muscle progenitors and the matrix in a necrotic context greatly alters their cytokine secretion profile, which leads to more rapid myoblast maturation via paracrine effects.

P-10

Phosphatidylcholine Metabolism and ACAT Affect the Trafficking of LDL-derived Free Cholesterol in Cholesterol-loaded CHO Cells

Chandra Landry (Supervisor: Dr. Thomas Lagace)

Purpose: In vitro studies have shown that the major membrane phospholipid phosphatidylcholine (PC) can positively influence the incorporation of cholesterol in lipid membranes. The influence of PC on the cellular trafficking of LDL-derived free cholesterol was investigated.
Methods/Results: Sterol regulatory-defective (SRD)-4 cells are Chinese hamster ovary (CHO)-derived fibroblasts that display vastly elevated rates for the synthesis and catabolism of PC. SRD-4 cells harbor two known gene mutations: a mutation in the functional allele for SCAP, resulting in defective feedback suppression of cholesterol biosynthesis; and a loss-of-function mutation in the functional allele for acyl-CoA:cholesterol acyl transferase (ACAT), an endoplasmic reticulum (ER)-localized enzyme that esterifies free cholesterol. Incubation of SRD-4 cells with 50 µg/ml low-density lipoprotein (LDL) for 18 h resulted in lysosomal accumulation of free cholesterol as revealed by filipin staining. This accumulation was not evident following LDL treatment of parental CHO7 cells, and was blunted in SRD-2 cells that express a constitutively-active form of SREBP-2 and overproduce cholesterol but have functional ACAT activity. Treatment of SRD-2 cells with LDL in the presence of an ACAT inhibitor 58-035 resulted in robust lysosomal cholesterol accumulation that was reversible upon drug washout, supporting that cholesterol trafficking in cholesterol-loaded cells is dependent on ACAT activity and, more specifically, ER free cholesterol levels. Lysosomal accumulation of LDL-derived cholesterol was prevented in SRD-4 cells supplemented with lyso-PC (50 µM), a substrate for PC synthesis through the reacylation pathway, and also in cells treated with bromoenol lactone (BEL), an inhibitor of phospholipase A2 implicated in bulk PC turnover. In a counter study, lysosomal LDL-derived cholesterol accumulation was induced in parental CHO7 cells using R-propranolol, which inhibits the conversion of phosphatidic acid to diacylglycerol (DAG), a substrate in the CDP-choline pathway. This blockage was also relieved through co-treatment with lyso-PC.
Conclusions: These studies support that PC to free cholesterol ratios in downstream organellar membranes can influence cholesterol trafficking out of lysosomal compartments in cholesterol-loaded cells.

P-11

Collagen:chitosan hydrogels for stimulation of angiogenesis in a type I diabetic mouse model: Potential use as a pre-vascularized ectopic site for islet transplantation

Joanne McBane (Supervisor: Dr. Erik Suuronen)

Purpose: Islet transplantation to treat type 1 diabetes (T1D) has shown varied long term success, due in part to poor blood supply, suggesting that pre-vascularization of the transplant site is needed. In the current study, we compared preformed collagen (1C) and collagen:chitosan hydrogels (2C), +/-circulating progenitor cells (CPCs), as materials to promote angiogenesis in a T1D (streptozotocin (STZ)-induced) nude mouse model.
Methods: CPCs were isolated from human peripheral blood mononuclear cells cultured on fibronectin for 4d. 1C or 2C (10:1 collagen:chitosan) hydrogels +/- CPCs were crosslinked using EDC/NHS. Matrices were tested *in vitro* for: CPC viability (live-dead assay); mechanical strength (Instron), crosslinks and fiber diameter (scanning electron microscopy); and degradation rate (collagenase). Mice were injected via the tail vein with a single dose of STZ (200mg/kg). One week post-injection, blood glucose readings were taken and a level of >10mmol was taken as a positive reading for hyperglycemia. Matrices +/- CPCs were implanted subcutaneously for up to 6 weeks in the STZ mouse model and evaluated for cytokine production (cytokine array), cell infiltration (hematoxylin and eosin staining) and expression of vWF (immunohistochemistry).
Results: After gelation at 37°C for 18h, live/dead staining showed greater CPC viability in the 2C gels compared to 1C gels (79% vs. 69%, $p<0.05$). There were no significant differences in the average fiber diameter (0.079mm and 0.073mm for 1C and 2C, respectively) or the initial gel size. The 2C gels were mechanically stronger than the 1C gels (0.6 vs. 0.4kPa at 30% strain, $p<0.05$), had more crosslinks (9.2 vs. 7.4/µm^2, $p<0.05$), and were degraded more slowly by 100U of collagenase (3h vs. 2h). Consequently, 2C gels could be retrieved after 6 weeks of subcutaneous implantation, whereas not all 1C gels were recovered. The 2C gels showed increased levels of pro-angiogenic cytokines at 1 and 2 week time points. By 6 weeks, the pro-angiogenic, anti-islet cytokine macrophage inflammatory protein gamma-1 was decreased for both gel matrices (~7-fold vs. 1 week). The 6 week explants trended toward more vWF$^+$ cells for the 2C vs. 1C gels; which correlates with the increased expression of VCAM-1 in 2C explants compared to 1C-CPCs gels at 6 weeks (cytokine array).
Conclusions: The mechanical, degradation and cytokine data all suggest that the 2C gel is a better candidate for use as a pre-vascularized ectopic islet transplant site.

P-12

Collagen-laminin hydrogels for delivery of insulin-producing tissue for the treatment of type 1 diabetes

Kimberly McEwan (Supervisor: Dr. Erik Suuronen)

Purpose: The lack of vasculature is a major limitation of islet transplantation therapy for the treatment of type 1 diabetes. Hydrogels are attractive bio-engineered materials for cell delivery, as they can provide an environment for cell survival and retention. The aim of this study was to develop and characterize a collagen-chitosan hydrogel to be used as an ectopic transplant site that will support vascularization and islet graft survival and function.
Method: Type-I collagen, chitosan (10:1 and 20:1 collagen:chitosan) and chondroitin sulfate-C were cross-linked with EDC/NHS, and then laminin (0, 10, 20 or 40µg/mL) was incorporated. Circulating progenitor cells (CPCs) in endothelial basal media (EBM) or islets in Ham's media were added. Live/dead staining was used to assess CPC and islet viability. Scanning Electron Microscopy (SEM): surface morphology, porosity and pore diameter were evaluated. Rheology: matrices were subjected to a constant shear rate to determine gelation properties. Mechanical Testing: compressive loading was applied to determine stiffness (modulus). Degradation: Degradation of hydrogels in water, PBS, collagenase (0.125U/mL) and amylase (220U/mL) was assessed.

Results: In 10:1 matrices, CPC viability was 1.3- and 1.4-fold greater with the addition of 20µg/mL and 40µg/mL of laminin, respectively (p=0.003, p=0.01) at 24h. At 48h, 20:1 matrices displayed 1.2-fold increases in viability with 20µg/mL and 40µg/mL laminin (p=0.03, p=0.0008). At 24h, islet survival was superior in the 20:1 matrix with 40µg/mL laminin (95.0±6.0%) compared to 10:1 matrix without laminin (70.9±0.03%, p=0.02). At 48h, islet viability in 20:1 matrix with 40µg/mL laminin was 80.3±4.0% compared to 69.3±6.4% without laminin (p=0.03). SEM illustrated smoother surfaces with 40µg/mL laminin compared to matrices without laminin. Pore diameter increased significantly with the addition of laminin compared to matrix-only ($p \leq 0.05$). Laminin had no significant effect on the materials' rheological properties. The elastic moduli of matrices synthesized with Ham's media (7.8-13.9kPa) were all significantly higher than those with EBM (1.2-6.6kPa). Also, matrices with higher chitosan content were stiffer. After 72h in collagenase, degradation of matrices with EBM was greater than those with Ham's ($p<0.05$). After 36h in amylase, all EBM matrices were completely degraded, whereas Ham's matrices had experienced little to no loss of weight ($p<0.05$).
Conclusions: Collagen-chitosan hydrogels can be modified with laminin to better support CPC and islet survival. Additives such as media and chitosan can be used to control physical properties. Therefore, hydrogels such as our matrix scaffold are promising as a strategy for improving the success of islet transplantation therapy.

P-13
Network-based Genomic Mapping highlights the influence of Central-Nervous System Pathways on Obesity
Majid Nikpay (Supervisor: Dr. Ruth McPherson)

Purpose: Given the modular nature of a complex phenotype, the underlying genetic factors share protein interaction (epistasis) and display coordinated gene expression; as such, we used these criteria to narrow the list of GWAS loci for obesity and investigate the underlying biological processes in a cohort of 958 obese (BMI $\geq$ 32 kg/m^2) and 869 lean (BMI $\leq$ 23 kg/m^2) subjects (OBLE study). We further repeated the analyses in two other samples selected from controls of OHGS_B2 (288 obese and 421 lean subjects) and OHGS_A2 (98 obese and 271 lean subjects) to verify our findings and determine the validity of our approach.
Method: Subjects in OBLE and OHGS_B2 were genotyped using 6.0 Affymetrix GeneChips (900K SNPs), and in OHGS_A2 genotyping was done using 500K SNP Array; moreover, the density of our SNP Maps were increased by genotype-imputation from the 1000 Genomes dataset. In each cohort, nominally associated loci ($P < 0.001$) were searched in STRING database and their protein interactions were extracted by specifying the highest confidence score (Score > 0.9). Next, genes that shared protein interactions were subjected to coexpression analysis using data from COXPRESdb database and those that formed a network of coexpressed (Pearson's $r < 0.5$) genes were selected. We further reduced the number of genes by performing the statistical test of epistasis and selecting those with significant interactions.
Results: We determined the expression of the resulting genes from OBLE (33 Genes), OHGS_B2 (12 Genes) and OHGS_A2 (12 Genes) across 65 normal human tissues using data from COXPRESdb and found that the identified genes in each study display high and coordinated expression profiles in cluster of brain-related tissues, and more particularly in parietal and frontal brain lobes; in addition, we noted that ≈ 50% of genes from each study have recorded synaptic function in the synapse databases, SynDB and G2C. Next, we determined the joint effect of these gene sets via the logistic kernel-machine-based test; we found that the resulting gene set in each cohort is highly associated with the obesity ($P < 10^{-12}$) further emphasizing the meaningfulness of identified gene sets and the practicability of our network-based approach.
Conclusion: Our findings support the notion that obesity is in part a central nervous system-mediated trait and show that the network properties of complex trait genes can be utilized to elucidate the genetic nature and the biological processes underlying a complex phenotype.

P-14
Synthesis and Characterization of Chitosan-Derived Hydrogels for Cardiovascular Tissue Engineering
Donna Padavan (Supervisor: Dr. Erik Suuronen)

Background: Ischemia is a central problem in cardiovascular disease and vascular complications associated with diabetes. Tissue engineered hydrogels have become popular scaffold platform materials for supporting cells and have demonstrated an ability to improve cell therapy in regenerative medicine. However, many hydrogels, although biocompatible, typically require chemical cross-linkers, limiting their therapeutic potential for transplanting cells, particularly as injectable materials. Thus, physically cross-linked hydrogels are attractive since they may improve the delivery of cells in a minimally invasive and non-toxic manner. This study aimed to develop chitosan-derived physically cross-linked hydrogels with tunable mechanical and cell responsive properties for supporting transplanted cells.
Methods: Two injectable materials were developed via ionic cross-linking: a) chitosan-derivative (HTCC) with sodium tripolyphosphate (TPP); and b) pure chitosan (PC) with beta-glycerophosphate disodium salt (βGP). Polymer hydrogels were characterized for the materials' chemical and physical properties, viscosity and mechanical properties. Cell-material interactions were evaluated using human blood-derived circulating progenitor cells (CPCs), human umbilical vein endothelial cells (HUVECs) and porcine islet cells, seeded onto the hydrogels and compared to their respective controls. Adhesion, viability and metabolic activity were evaluated on days 1, 2 and 7 using standard adhesion, viability (live/dead) and WST-1 assays. Additionally, hydrogel embedded islet cells and their insulin production were quantified using flow cytometry and enzyme-linked immunosorbant assay (ELISA).
Results: PC-βGP was less viscous (5.5±0.5Pa•s) at 37°C compared to HTCC-TPP (11±4Pa•s). The mean compressive stress and elastic modulus obtained from the regression analysis fit were calculated at 12% strain for PC-βGP and HTCC-TPP hydrogels (n=7) and were found to be 0.45±0.16kPa and 6.33±0.87kPa, and 0.06±0.007kPa and 0.05±0.01kPa, respectively. This indicated that PC-βGP was significantly stiffer than HTCC-TPP. Morphology revealed uniform pore distribution for both hydrogels, with HTCC-TPP having higher (14%) porosity. Gels degraded 4× faster in alpha-amylase (pH 7, 37°C, 250IU/ml) than in PBS over 7 days. Cell compatibility was assessed and the number of CPCs and HUVECs adherent on HTCC-TPP was less compared to PC-βGP ($p \leq 0.001$). Live/dead assays revealed comparable

cell viability (>70%) between gels, and WST-1 showed greater cell metabolic activity on PC-βGP ($p \leq 0.05$). ELISA for insulin and flow cytometry labeling showed similar trends by 7 days.
Conclusion: Chitosan-derived microgels are promising as delivery vehicles and suitable for supporting multiple cell types for cardiovascular and islet transplantation tissue engineering therapies.

P-15
Cathepsin G and atherosclerotic lesion complexity
Naimeh Rafatian (Supervisors: Dr. Frans Leenen and late Dr. Stewart Whitman)

Purpose: Cathpesin G is a serine protease with a broad range of catalytic activities including production of angiotensin II, degradation of extracellular matrix and cell-cell junctions , modulation of chemotactic responses and induction of apoptosis. Cathepsin G mRNA expression is increased in human coronary atheroma versus the normal vessel, but its role in atherosclerosis development has not been studied.
Methods: To assess how cathepsin G modulates atherosclerosis cathepsin G knockout (Cstg $^{-/-}$) mice were bred with apo lipoprotein E knockout (Apoe $^{-/-}$) mice to obtain Ctsg$^{+/-}$ Apoe$^{-/-}$ and Ctsg$^{+/+}$Apoe$^{-/-}$. Ctsg$^{+/-}$ Apoe$^{-/-}$ male mice and their wild type littermates were fed with cholesterol rich "western" diet for 8 weeks to assess early atherosclerotic lesions.
Results: Heterozygous cathepsin G deficiency reduced cathepsin G activity in bone marrow cells by 70% but this reduction did not attenuate generation of angiotensin II in bone-marrow derived macrophages or atherosclerotic lesions .Atherosclerotic lesions were compared in male Cstg $^{+/-}$ Apoe $^{-/-}$ and Cstg $^{+/+}$ Apoe $^{-/-}$ mice after 8 weeks on high fat diet. The atherosclerotic lesion areas in either the aortic root or aortic arch did not differ between both genotypes. Cathepsin G partial deficiency also did not affect total cholesterol content and lipoprotein profile. However, Cstg $^{+/+}$ Apoe $^{-/-}$ mice did show a higher percentage of complex lesions in the aortic root, larger necrotic core areas, a greater number of apoptotic TUNEL-positive nuclei and higher plasma levels of interleukin 5 and interleukin 9 compared to Cstg$^{+/-}$Apoe$^{-/-}$ littermates.
Conclusion: Cathepsin G partial deficiency appears to attenuate the progression of early atherosclerotic lesion in Apoe$^{-/-}$ mice to more complex lesion.

P-16
Initial Evaluation of a Spline Model for Sampling of the Right Ventricle Myocardium from Cardiac PET Images
Simisani Takobana (Supervisors: Ran Klein- Ottawa Heart Institute, Professor Andy Alder-Carleton University, Robert DeKemp-Ottawa Heart Institute)

Background: Conditions such as pulmonary hypertension usually alter right ventricular (RV) physiology and anatomy, in most cases making it hypertrophic and dysfunctional. Because of a wide range of RV anatomies among human and animals, with normal and hypertrophic hearts a spline model must be general. However, the model should minimize the number of control points as well as their degrees of freedom for computational efficiency and usability.
Purpose: To evaluate a proposed 11 spline points model with 12 degrees of freedom for sampling the RV in cardiac PET images.
Methods: A sample set of 5 normal and 5 hypertrophic human, and 5 normal and 5 hypertrophic rat hearts FDG PET images was used. The RV model was manually fit to each image, and the fit was evaluated. A pass was granted when the model was judged by the operator to sufficiently trace the RV mid-myocardium and appropriately intersect the LV.
Results: In normal rats, the RV was difficult to visualize due to its thinner wall, proximity to the thicker LV, and low image resolution. In all human and hypertrophic rat hearts the model was sufficient for tracing the RV.
Conclusions: The proposed model is sufficiently flexible to describe normal and hypertrophic hearts in human and rat populations. It is possible that a simpler model, with fewer degrees of freedom may be sufficient, while further reducing the model complexity.

P-17
MicroPET imaging of Cardiac FTHA uptake in mice: Effect of Isoflurane Anaesthesia
Presented by Stephanie Thorn for Aleks Brezar (Supervisor: Dr. Jean DaSilva)

Background: The extent and progression of metabolic changes in cardiac disorders are commonly investigated using transgenic mouse models. The PET F-18 labeled fatty acid analog Fluoro-6-Thia-Heptadecanoic acid (FTHA), has previously been reported to measure free fatty acid (FFA) uptake in the normal mouse myocardium using ex vivo biodistribution procedures (Degrado, 1991). In this preliminary study, we investigated the use FTHA to measure cardiac FFA with non-invasive microPET imaging and optimize methodology with isoflurane anaesthetic.
Methods: Optimization of the FTHA (0.2-0.3 mCi) imaging procedures were conducted using a Siemens Inveon MicroPET scanner in normal 3 months old FVB mice: n=3 60 min isoflurane scan, n=4 awake for 30 min and then scanned for 30 min, n=3 awake 60 min prior to a 30 min scan. Regions of interest (ROIs) were drawn on the heart and liver with the Inveon Research software. Tissue uptake (% injected dose per gram of tissue or %ID/g) was confirmed with ex vivo biodistribution data and compared to n=3 mice awake for 60 and 90 min. Tissue uptake data was correlated to blood glucose, plasma insulin and FFA levels and cardiac FFA levels.
Results: 60 min of isoflurane resulted in a higher liver uptake of FTHA at 33 %ID/g with low uptake in the heart at 12 %ID/g with a heart to liver ratio of 0.37. By decreasing the anaesthesia duration to 30 min after an initial 60 min awake uptake period, FTHA uptake was increased in the heart, with a heart: liver ratio of 1.5. These results were comparable to a heart: liver uptake in the 90 min awake ex vivo biodistribution data of 1.4. There was no correlation in FTHA results with blood glucose, plasma insulin and free fatty acids levels.
Conclusion: There is a significant effect of isoflurane during the initial uptake period of FTHA reducing cardiac uptake while increasing uptake in the liver. Although the heart can be imaged under these conditions, increasing liver uptake reduces quantification of the inferior wall due to significant activity spillover. This preliminary study is the first to show microPET imaging of FTHA in the mouse myocardium and to investigate the effect of isoflurane on cardiac fatty acid metabolism. The optimized procedure will allow for further serial non-invasive imaging of FTHA uptake in mouse cardiac disease models.

P-18

Single cell encapsulation of cardiac stem cells to enhance acute engraftment

Everad Tilokee (Supervisors: Dr. Darryl Davis)

Purpose: Cellular cardiomyoplasty using *ex vivo* proliferated cardiac stem cells (CSC) is an emerging treatment option in the management of heart failure; however, regeneration is limited by cell engraftment and survival. Given that studies have shown enhanced functional benefits following improvements in acute engraftment, we explored the capacity of single cell encapsulation to boost acute CSC proliferation/survival with the ultimate goal of enhancing engraftment after intra-myocardial injection.
Methods and Results: Human atrial appendages were obtained from patients undergoing clinically-indicated surgery. Resident CSC cultures were established and CSCs were encapsulated in agarose capsules containing immobilized matrix proteins to enhance cell-matrix survival signals. CSCs encapsulated within fibronectin and fibrinogen supplemented capsules demonstrated increased viability as compared to standard adherent and suspension culture (1.7±0.7 vs. 1.3±0.1 and -0.9±0.1 fold increase, respectively; $p<0.05$). Capsules were further supplemented with type IV collagen to mimic the matrix microenvironment of stem cell niches within the native heart. While this strategy increased the initial viability of encapsulated CSCs (+167 ±10%, $P<0.05$ vs. standard encapsulation), collagen supplementation did not provide for additional proliferation within the capsule (1.2±0.3 fold increase, p=ns). Interestingly, decreasing the agarose content within the capsule provided a means of engineering early CSC migration from the capsule (52.3±6.5% vs. 5.0±3.4% extra-capsular CSCs 24 hours post encapsulation for 2.5 and 3.5% agarose, respectively; $p<0.05$).
Conclusions: Encapsulation of CSCs in agarose supplemented with immobilized matrix proteins boosts *in vitro* proliferation/survival by providing vital extra cellular matrix clues that prevent detachment induced apoptosis (or anoikis). While mirroring the natural environment of cardiac niches promotes the initial recovery of CSCs, it does not enhance proliferation of cells within the capsules. Finally, manipulation of capsule constituents supplies a means of altering the CSCs migration from the capsule- potentially altering the kinetics of CSC delivery to the myocardium after transplantation.

P-19

Evaluation of a New, Clinically Relevant Biopolymer Matrix for Vasculogenesis and Myogenesis in the Setting of Acute Myocardial Infarction

Hadi Toeg (Supervisor: Dr. Marc Ruel)

Purpose: This project was undertaken to elucidate the underlying mechanism involved in myocardial regeneration and cardiac remodelling when administration of porcine small intestinal submucosa-extracellular matrix (SIS-ECM) biomaterial with or without Circulating Angiogenic Cells (CACs) into a mouse myocardial infarction (MI) model would improve the recruitment and growth of endogenous cells. The potential role of the injectible SIS-ECM on enhancing angiogenesis, myogenesis, myocardial recovery, and functional changes in the infarcted myocardium was evaluated.
Methods: Female 9-10 week old C57BL/6J mice had their left anterior descending coronary artery ligated and a week after post infarction, animals were randomly allocated to receive echo-guided intramyocardial injection of either PBS alone (control, n=6) or SIS-ECM alone (n=6). CACs were isolated from the bone marrow of age matched C57BL/6J male mice. Mice were sacrificed on day 28 post ligation and histology (ventricular wall thickness, arteriolar density), immunoshistochemistry (c-kit, α-smooth muscle actin), and echocardiography (left ventricular ejection fraction [LVEF]) were performed and analyzed. In vitro studies looking at proliferation, migration, and adhesion of CACs cultured on SIS-ECM were performed.
Results: CACs cultured on SIS-ECM matrix resulted in higher proliferation (Ki-67), adhesion, and migration of these angiogenic cells (n=2). Post ligation day 7 baseline LVEF was equivalent in all groups. On day 28 post treatment, LVEF was improved with the SIS-ECM treatment group (36%) as compared to PBS-control (31%). LV wall thickness was better preserved in the matrix group (compared to PBS-control (n=3) and was able to maintain elevated number of C-kit positive cardiac progenitor cells. Arteriolar density was greatest in the matrix treatment versus PBS-control. There was a trend for larger in size and increased arteriole counts with matrix treatments (n=3).
Conclusions: Intramyocardial delivery of SIS-ECM matrix improves cardiac function, partially restores myocardial viability, and preserves LV wall mass in a mouse MI model. Thus, implicating a minimally invasive clincally relevant role of SIS-ECM injection in cardiac regeneration.
Keywords: Regeneration, Myocardial Infarction, Stem cells

P-20

Over-expression of glyoxalase-1 in the bone marrow reverses defective neovascularization in streptozotocin-induced diabetic mice

Branka Vulesevic (Supervisors: Dr. Erik Suuronen and Dr. Ross Milne)

Purpose: Methylglyoxal accumulates in diabetes and is thought to disrupt bone marrow (BM) cell function and contribute to defective neovascularization. The objective of this study was to assess whether over-expression of glyoxalase-1 (GLO1), a methylglyoxal-metabolizing enzyme, could reverse BM defects and restore neovascularization in ischemic tissue of streptozotocin-induced diabetic mice.
Methods: BM cells from enhanced green fluorescent protein (GFP) mice that over-express human GLO1 were used to reconstitute the BM of wild-type (WT) streptozotocin-treated mice (termed 'GLO1-diabetics'). Streptozotocin-treated and non-diabetic recipients of GFP BM served as controls ('WT-diabetics' and 'non-diabetics', respectively). Following 6wks for marrow reconstitution, hindlimb ischemia was induced.
Results: The mobilization of GFP^+ cells expressing CXCR4, VEGFR2 or c-kit GFP^+CXCR4 was greater (up to 6-fold) in GLO1-diabetics compared to WT-diabetics, but not different from non-diabetics over 2 wks. Perfusion was greater in GLO1-diabetics (1.1±0.1) and non-diabetics (1.1±0.2) after 2 wks, compared to WT-diabetics (0.4±0.1).Western blot analysis for the GFP protein confirmed the increased presence of BM cells recruited to the ischemic tissue in the GLO1-diabetic mice (by 1.7-fold) and non-diabetic mice (by 1.8-fold) versus the WT-diabetics, demonstrating successful recruitment and engraftment of BM cells. Compared to

WT-diabetics, GLO-diabetics demonstrated 3.3-fold greater recruitment of $CXCR4^+$ cells from BM to the hindlimb, and 3.3-fold higher arteriole density than the WT-diabetics. *In vitro* testing showed increased viability of BM cells from GLO1-diabetic and non-diabetic mice after 24h culture in hyperglycemic and hypoxic conditions, compared to BM of WT-diabetics.
Conclusions: This study demonstrates the contribution of methylglyoxal to defective BM function and neovascularization in diabetes and identifies GLO1 as a potential therapeutic target.

P-21
Deletion of Klf13 in mice leads to endocardial cushion defects
Abir Yamak (Supervisor: Dr. Mona Nemer)

KLF13 is a member of the Krüppel-like transcription factors that are important regulators of cell proliferation and differentiation. Several KLF members are expressed in the heart in a spatial and temporal specific manner.
KLF13 is highly enriched in the developing heart where it is found in both myocardial and endocardial cells. In myocytes, it interacts with GATA4 and regulates the A- and B-type natriuretic peptide genes, *NPPA* and *NPPB*.
In *xenopus*, knock down of KLF13 causes developmental heart defects which indicates an important role for KLF13 in heart morphogenesis. To test whether this role is evolutionary conserved in the mammalian heart, we deleted the KLF13 gene in transgenic mice using homologous recombination. Mice lacking both KLF13 alleles are born at reduced frequency; variable cardiac phenotypes are observed in these knockouts mainly endocardial cushion defects including "Goose-neck" deformity and atrioventricular (AV) valvular abnormalities. Epithelial-mesenchymal transformation (EMT) seems to be affected in these mice and they have reduced proliferation in the AV cushion. Surviving KLF13 null mice have several structural cardiac anomalies. *NPPB* mRNA levels are decreased by 50% and expression of several cardiac genes is altered.
Our data uncover a role for a new class of transcription factors in heart formation and point to KLF13 as a potential congenital heart disease causing gene.

P-22
Identification of GATA4 regulatory mechanisms associated with heart development and disease
Jamie Whitcomb (Supervisor: Dr. Mona Nemer)

GATA4 is a member of the GATA family of zinc-finger transcription factors that has wide-ranging roles in cardiac development and hypertrophy. Point mutations of GATA4, which frequently result in cardiac malformations such as septal and valvular defects, have been shown to result in impaired DNA binding and protein-protein interactions. These impaired interactions frequently give rise to congenital heart disease, which currently represent 25% of all human congenital defects. Given the importance of GATA4 in the cardiac gene program, it is therefore important to gain insight into both positive and negative regulators of GATA4, including post-translational modifications and protein-protein interactions. In this study, we aim to determine sites on the GATA4 gene that are post-translationally modified as well as novel interacting proteins that regulate GATA4 gene and protein function. As endothelial cardiac precursor cells are known to form the septa and valves of the heart, where improper formation problems frequently arise, TC13 endocardial cardiac precursor cells were chosen as a model cell line for this study. Nuclear extracts of TC13 cells that were retrovirally transduced with TripleFlag-GATA4 were obtained and GATA4 was then immunoprecipitated and purified. These samples will be analyzed via HPLC-ESI-MS/MS to determine sites on the GATA4 protein that are post-translationally modified. Likewise, GST-pull down assays using extracts of TC13 cells will be used to determine novel GATA4 interacting partners important to the early cardiac gene program. This study will shed light on the critical processes by which GATA4 is modified in order to properly induce cardiac development and will help to elucidate the molecular mechanisms leading to congenital heart disease.

P-23
Stimulation of macrophage apoptosis in cIAP2 x ApoE double-knockout atherogenic mice with tumour necrosis factor alpha
Presented by Lyne Sleiman for Alex Norgaard (Supervisors: Dr. Rob Beanlands and Dr. Tom Moon)

Background: Atherosclerosis is an inflammatory process important in human cardiovascular diseases. It involves many cellular pathways, including those for apoptosis. We sought to determine if the absence of the inhibitor of apoptosis proteins (specifically cIAP2) would alter the level of apoptosis occurring in peritoneal and bone marrow-derived macrophages from mice on an ApoE-/- background.
Methods and Results: Cells were treated with TNFα (20 pg/mL to 100 ng/mL) for 48 h. The amount of apoptosis was assessed indirectly by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Significant differences in viability were observed in knock-out bone marrow-derived macrophages compared to wild-types at high concentrations of TNFα (50 and 100 ng/mL). The 12-week diet significantly decreased viability of knock-out peritoneal macrophages with high TNFα exposure.
Conclusion: cIAP2 is an important inhibitor of apoptosis and its loss decreased the viability of macrophages treated with TNFα. Further studies are needed to more fully characterize the process of apoptosis these cells undergo.

CLINICAL SCIENCE POSTER PRESENTATIONS

P-24
Left atrial volume index during ventricular diastasis assessed by cardiac computed tomography is an incremental predictor adverse events
Mohammed Alam (Supervisor: Dr. Benjamin Chow)

Purpose: Computed tomographic (CT) coronary angiography (CTA) is increasingly being accepted as a key diagnostic modality for the non-invasive detection of coronary artery disease (CAD). To minimize patient radiation exposure prospective-ECG gated image acquisition algorithms are being increasingly used whereby image

acquisition is restricted to ventricular diastasis when cardiac motion is at a minimum. However, this leads to the loss of left ventricular (LV) and left atrial (LA) functional information. Previous studies have shown that assessment of LA volume index (LAVI) has incremental prognostic value in CAD patients. However, prognostic value of LAVI during ventricular diastasis has never been investigated before. The objective of the present study was to determine the prognostic ability of LAVI assessed during ventricular diastasis in predicting adverse events.
Methods: The Cardiac CT Registry data base at the University of Ottawa Heart Institute was queried and 101 patients (constituted test population) with adverse events (all-cause mortality and troponin positive acute myocardial infarction) on follow up were identified. A matched control list (matched according to the Morise score: the score based on clinical findings) of 101 patients (constituted control population) with no adverse events on follow up was also generated from the same registry. Images were reconstructed at the 75% phase (mid diastasis) and LA volume index (LAVI: LA volume indexed to body surface area) was calculated in both groups. Prognostic value of LAVI was assessed for both univariable and multivariable associations with all-cause mortality and acute myocardial infarction as combined end point using Cox proportional hazard models.
Results: Baseline characteristics of the test and control populations were similar. The mean follow up duration was 20 ±12 months. LAVI was significantly larger (118.68 ± 40.24 vs 100.27 ± 27.93; p=0.0002) in patients who experienced adverse events on follow up. LAVI was both univariable (p=0.001) as well as multivariable predictor (p=0.001) of adverse events on Cox regression analysis.
Conclusions: Patients experiencing adverse events (all-cause mortality and troponin positive acute myocardial infarction) on follow-up have significantly larger LAVI during ventricular diastasis. LAVI assessed during ventricular diastasis by CT is an incremental predictor of adverse events. This additional prognostic information from existing prospective ECG-gated CTA data sets may be provided to clinicians.

P-25
Aortic Root Geometry in Bicuspid Aortic Insufficiency versus Stenosis: Implications for Valve Preservation and Repair

Talal Al-Atassi (Supervisor: Dr. Munir Boodhwani)

Purpose: While bicuspid aortic valve (BAV) insufficiency is invariably associated with leaflet abnormalities, the contribution of concomitant aortic annular and root disease remains unclear. We compare the aortic root geometry between BAV insufficiency (AI) and stenosis (AS).
Method(s): Consecutive patients presenting for surgical intervention for BAV insufficiency (n = 39) were compared with randomly selected patients with BAV stenosis (n = 39). Clinical and transesophageal echocardiographic (TEE) data was collected. End-diastolic aortic diameters were measured at the ventriculo-aortic junction (VAJ), aortic root, sinotubular junction (STJ), and ascending aorta (AA). Aortic root height (VAJ to STJ) was also assessed.
Results: AI patients were younger and more likely to be male compared to AS patients (mean age in years 48 vs. 63, p<0.001; 87% vs. 63% male, p=0.012, respectively). The VAJ, sinuses of Valsalva, and STJ diameters were significantly larger in AI patients as compared to AS patients (mean diameters in mm ± standard error: 30±0.6 vs. 26±0.5, p<0.001; 40±1.0 vs. 34±0.7, p<0.001; 34±1.0 vs. 30±0.7, p= 0.004, respectively). The mean AA diameter in the AI group was statistically similar to the AS group (33±0.9 mm vs. 34±1.0 mm, p=0.50). Annular interventions led to a reduction of > 4 mm in VAJ diameter in all patients.
Conclusions: Despite similar AA diameter, aortic annulus and root dimensions are significantly larger in patients presenting with BAV insufficiency compared to stenosis. Alterations in aortic root geometry are important contributors to the pathophysiology of BAV insufficiency and require correction for a successful repair.

P-26
Integrin and CMR Imaging of the Extent of SCAR in Hypertrophic Cardiomyopathy

Myra Cocker (Dr. Terrence Ruddy)

Background: Patients with hypertrophic cardiomyopathy are at risk for developing heart failure, secondary to the release of stress-responsive trophic factors that promote collagen synthesis, disarray and hypertrophy. Cardiovascular magnetic resonance (CMR) imaging with T1-weighted late gadolinium enhancement (LGE) can be utilized to image the extent of focal regions of fibrosis. However, focal fibrosis detected by LGE may not be an accurate surrogate marker of patient prognosis nor cardiac remodeling, given that the disease is more diffuse in the setting of HCM. Thus, CMR may underestimate the extent of myocardial fibrosis compared to autopsy. Within the family of vitronectin integrin receptors which mediate cell-to-cell and cell-matrix interactions, αvβ3 is unique in that its expression increases during ischemic injury, co-localizes with myofibroblasts and is correlated with "new" collagen. A novel ^{99}Technetium compound (^{99m}Tc-NC100692, GE healthcare) that binds with high affinity to αvβ3 has been developed. ^{99m}Tc-NC100692 uptake may be a sensitive and accurate marker of myocardial fibrosis. In this investigation, we compared the distribution of ^{99m}Tc-NC100692 myocardial uptake to CMR LGE in patients with hypertrophic cardiomyopathy.
Methods: 5 patients were prospectively recruited. HCM was established by echocardiography. Patients underwent SPECT ^{99m}Tc-NC100692 and T1-weighted LGE imaging. ^{99m}Tc-NC100692 was assessed visually for the presence or absence of myocardial uptake using a three-point scale for the AHA 17-segment model, and LGE was also assessed using the 17-segment model for the presence or absence of enhancement.
Results: Overall, 85 left ventricular segments were assessed in 5 patients. Myocardial hypertrophy was observed in 14 segments. Of these 14 segments, LGE was present in 9 segments and high-level of ^{99m}Tc-NC100692 uptake was observed in 5 segments. In one patient, the apical segment also had increased ^{99m}Tc-NC100692 uptake without evidence for hypertrophy or LGE. In addition, diffuse low grade ^{99m}Tc-NC100692 uptake was observed in 79 segments with lack of evidence for hypertrophy or LGE.
Conclusion: There is evidence for low-grade ^{99m}Tc-NC100692 uptake in patients with hypertrophic cardiomyopathy. This may be a marker of diffuse myocellular disarray and potentially fibrosis. High grade ^{99m}Tc-NC100692 uptake mirrored hypertrophic myocardium that had evidence for scar.

P-27

Exercise Stress FDG Imaging as a More Sensitive Indicator of the Extent of Myocardial Ischemia

Taylor F. Dowsley (Dr. Terrence Ruddy)

Purpose: Single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is established as a sensitive indicator for the detection of obstructive CAD. However in a substantial number of patients with an abnormal SPECT-MPI study, the extent of abnormal perfusion is underestimated. This relates to several factors including non-linear uptake of myocardial tracer and the fact that relative, not absolute, perfusion is assessed such that often only the most severe areas of relative perfusion abnormality are discernable. The predominant energy substrate for the heart during normal metabolism is fatty acids. During an ischemic insult there is rapid and profound upregulation of glucose extraction from the circulation via Glut 4-mediated transport. The purpose of the present study was to determine if PET imaging of FDG uptake during exercise stress will identify areas of stress-induced ischemia and be more accurate at defining the extent of myocardium involved compared with stress MPI.
Methods: A total of 8 patients have been recruited to undergo FDG imaging including 4 normals and 4 with CAD. The extent of ischemic myocardium was compared between FDG imaging and relative perfusion imaging with PET or SPECT MPI and correlated with areas of obstructive CAD on cardiac computed tomography angiography (CTA) or invasive coronary angiography.
Results: In normals, there was no focal myocardial uptake of FDG consistent with the absence of ischemic myocardium. Patients with stress-induced reversible perfusion defects on SPECT-MPI suggestive of ischemia also showed corresponding focal uptake of FDG. However the extent of myocardium involved was greater for stress FDG PET than SPECT-MPI. In one representative example, SPECT-MPI showed evidence of ischemia in the RCA territory whereas there was focal FDG uptake in both the RCA and LCX territories. CTA showed significant obstructive disease in both the RCA and LCX territories indicating a more accurate representation from FDG PET than SPECT-MPI.
Conclusion: These results suggest that exercise FDG PET imaging is feasible and shows potential to be a more sensitive indicator of the extent of myocardial ischemia than SPECT-MPI.

P-28

Prognostic Value of Coronary Calcification Detected by Cardiac Computed Tomography in Patients with Renal Dysfunction

Girish Dwivedi (Supervisor: Dr. Benjamin Chow)

Purpose: Coronary artery calcification (CAC) may represent an important mediator of the association between renal dysfunction and cardiovascular events. Previous studies have revealed incongruent results with regards to association between CAC detected on multislice computed tomography (CT) and renal dysfunction of various grades. Moreover, incremental prognostic value of CAC over other clinical variables including various grades of renal dysfunction has not been investigated.
Methods: A large international multicenter registry (CONFIRM Registry) was queried, and patients with CAC, left ventricular ejection fraction and creatinine data were screened. Patients with a history of myocardial infarction, coronary revascularization, or cardiac transplantation were excluded. The National Cholesterol Education Program (NCEP)-Adult Treatment Panel III risk, CAC severity on cardiac CT (based on 5 point Agaston score: 0;1-100;101-400; 401-1000; >1000) was calculated for each patient. Renal function was estimated using the estimated glomerular filtration rate (eGFR) formula.
Results: 27,125 patients underwent cardiac CT at 12 participating centres, with a total of 4529 patients meeting the analysis criteria. Follow-up was available for 4497 (99.3%) patients ((median follow-up 18.6 months). All-cause mortality occurred in 53 patients. All cause mortality increased with worsening levels of CAC across the entire spectrum of renal function. Multivariate Cox proportional hazards models revealed that both CAC (hazard ratio 1.57; 95% CI 1.28 to 1.94) and eGFR (hazard ratio 1.85; 95% CI 1.28 to 2.66) were independent predictors of all cause mortality after accounting for NCEP risk score.
Conclusions: Our results demonstrate that cardiac CT measures of CAC severity provides effective risk stratification across the entire spectrum of renal function and incorporation of CAC severity provides incremental value for predicting all-cause mortality over routine clinical predictors.

P-29

Predictive Value of Cardiac Computed Tomography and the Impact of Renal Function on All Cause Mortality

Girish Dwivedi (Supervisor: Dr. Benjamin Chow)

Purpose: Patients with chronic kidney disease have worse cardiovascular prognosis than those without. The prognostic value of computed tomographic coronary angiography (CCTA) in patients with varying degrees of renal impairment has not been investigated. The aim of this study was to evaluate the prognostic implications of CCTA in patients with impaired renal function.
Methods: A large international multicenter registry (CONFIRM Registry) was queried, and CCTA patients with left ventricular ejection fraction (LVEF) and creatinine data were screened. Patients with a history of myocardial infarction, coronary revascularization, or cardiac transplantation were excluded. The National Cholesterol Education Program Adult Treatment Panel III risk and CCTA was evaluated for coronary artery disease (CAD) severity (normal, non-obstructive, or obstructive CAD) and LVEF <50%. Renal function was calculated with the Modified Diet in Renal Disease equation. Patients were followed for an end point of all-cause mortality.
Results: Among 5655 patients meeting study criteria, follow-up was available for 5572 (98.9%) patients (median follow-up 18.6 months). All cause mortality (66 deaths) significantly increased with every 10 units decrease in renal function (hazard ratio 1.23, 95% CI 1.07 to 1.41). All-cause mortality occurred in 0.33% of patients without coronary atherosclerosis, 1.82% of patients with nonobstructive CAD, and 2.43% of patients with obstructive CAD. Multivariate Cox proportional hazards models revealed that impaired renal function (hazard ratio 2.29, 95% CI 1.65 to 3.18), CAD severity (hazard ratio 1.81, 95% CI 1.31 to 2.51) and abnormal LVEF (hazard ratio 4.16, 95% CI 2.45 to 7.08), were independent predictors of all cause mortality, after accounting for risk factors.

Conclusions: CCTA measures of CAD severity and LVEF provide effective risk stratification across a wide spectrum of renal function. Renal dysfunction, CAD severity and LVEF have additive value for predicting all-cause death in patients with suspected obstructive CAD.

P-30
Short-term repeatability of resting myocardial blood flow measurements using rubidium-82 PET imaging.

Matthew Efseaff (Supervisor: Dr. Robert A. deKemp)

Objectives: The goal of this study was to optimize the same-day repeatability of rubidium-82 (^{82}Rb) myocardial blood flow (MBF) imaging with a highly automated analysis program using image-derived input functions and dual spillover corrections.
Methods: Test-retest repeatability of resting left-ventricle MBF was measured in patients (n = 27) with suspected coronary artery disease and healthy volunteers (n = 9). The effects of scan-time, reconstruction and quantification methods were assessed with correlation and Bland-Altman repeatability coefficients.
Results: Factors affecting rest MBF included gender, suspected coronary artery disease, and spillover correction ($p < 0.001$). Significant test-retest correlations were found using all analysis methods tested ($r > 0.79$). The best repeatability coefficient for same-day MBF was 0.20 mL/min/g using a 6 min scan-time, iterative reconstruction, dual spillover correction, resting rate-pressure product adjustment, and left atrium input function. This protocol was significantly less variable than protocols using filtered back projection reconstruction, longer scan-time, no spillover correction, or left ventricle input function.
Conclusion: ^{82}Rb PET MBF can be measured repeatably using a 6 min scan length, iterative reconstruction, dual spillover correction, rate-pressure product adjustment, and an image-derived input function in the left atrium.

P-31
Aortic Plaque Inflammation and Aortic Dilatation

Jeewanjit S. Gill (Supervisor: Dr. Terrence Ruddy)

Purpose: To determine the feasibility of assessing aortic atherosclerotic plaques with 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG PET) / CT hybrid imaging and to determine the relationship between FDG uptake and regional aortic dilatation.
Methods: We recruited 6 patients from the Stroke Clinic Database at The Ottawa Hospital. The patients had the following inclusion criteria: 1) age > 60, 2) Diagnosis of stroke or TIA made by a stroke specialist within 90 days, 4) Carotid Doppler, CTA or MRA confirming the presence of bilateral atherosclerotic disease resulting in carotid stenosis of any degree, 5) 12 lead ECG or Holter monitor confirming the absence of atrial fibrillation. The exclusion criteria includes: 1) TIA or stroke in the vertebrobasilar system, 2) Index event was primary haemorrhage, 3) History of intermittent atrial fibrillation, 4) Cardiac source of embolus suspected as cause of index event (artificial valve, segmental or global LV dysfunction, congenital cardiac defect), 5) Diagnosis of vasculitis, dissection, or non-atherosclerotic carotid disease, 6) Sinovenous thrombosis, endocarditis or hypercoagulable state.
Each patient underwent CT, MRI, and FDG PET scans. CT was used to measure aortic volume and FDG PET was used to quantify the level of inflammation within aortic atherosclerotic plaque on a slice-by-slice basis. There were over 120 slices analyzed throughout the entire aorta of each patient.
Results: Among the patients we recruited in this study, FDG PET/CT hybrid imaging can be successfully used to assess inflammation within aortic plaques. There is a positive but weak correlation between inflammatory atherosclerotic plaques and increased aortic volume in the descending aorta ($r^2 = 0.118$). No correlation was seen in the ascending aorta and a weak negative correlation ($r^2 = 0.101$) was observed in the aortic arch.
Conclusion: Plaque inflammation can be imaged and quantified on FDG PET/CT hybrid imaging. Plaque inflammation (SUV > 1) was found throughout the aorta and was most increased in the descending aorta. Plaque inflammation was weakly correlated with dilatation of the descending aorta, supporting the concept that inflammation is a dynamic and transient process whereas anatomic changes are progressive and persistent.

P-32
Clinical Outcomes in ST-Elevation Myocardial Infarction Patients Treated with the Pharmacoinvasive Strategy in the Ottawa STEMI Program

Nita Guron (Supervisor: Dr. Michel Le May)

Background: The pharmacoinvasive strategy has been shown to be superior to fibrinolysis alone in reducing mortality in patients with ST-Elevation myocardial infarction (STEMI). It has been recommended that STEMI programs adopt such a strategy when primary percutaneous coronary intervention (PCI) is not an option. There is currently limited real-world data on this approach. We sought to determine the outcomes of patients treated with a pharmacoinvasive approach used in the Ottawa Regional STEMI system.
Methods: The University of Ottawa Heart Institute's (UOHI) Regional STEMI Program has evolved to use primary PCI for 9 hospitals located within 60 km of the PCI centre, and a pharmacoinvasive strategy for 7 community hospitals beyond this limit. We studied a population consisting of STEMI patients referred to the UOHI between April 2009 and May 2010 who were treated with the pharmacoinvasive strategy. The primary endpoint consisted of a composite of death, re-infarction, or stroke during index hospitalization. Secondary endpoints included TIMI bleeding during hospitalization and death at 180 days.
Results: We identified 79 confirmed STEMI patients who were transferred to the UOHI after receiving fibrinolytic therapy (94% of patients received tenecteplase, while 6% received reteplase) and who had a coronary angiogram performed within 24 hours. Amongst these patients, 75% were male, 20% had diabetes, 48% had hypertension, and 53% were active smokers. The median age was 61 ± 11yrs. Location of the infarct was anterior in 50% of cases and 89% of patients presented as Killip class I. PCI was performed in 89% of patients, coronary artery bypass surgery (CABG) was performed in 8.6% of patients, and 3.4% of patients were treated with medical therapy only after their angiogram (no intervention performed). Of the 79 patients, 42% required rescue PCI due to failure of adequate reperfusion post-fibrinolysis. Initial angiography revealed baseline

TIMI 3 flow in 51% of patients and post-intervention TIMI 3 flow was achieved in 97% of patients. The primary outcome occurred in 2 (2.6%) patients during hospitalization; death occurred in 1 patient (1.3%), and stroke in 1 patient (1.3%). No patients experienced re-infarction during index hospitalization. At 180-day follow-up, death occurred in 2 (2.5%) patients and re-infarction occurred in 1 (1.3%). TIMI major non-CABG bleeding occurred in 2.5% of patients, while 6.3% experienced TIMI minor non-CABG bleeding. Of the 6 patients who underwent CABG, a major CABG-related bleed occurred in 1 (17%) patient during hospitalization.
Conclusion: Our research demonstrates that treating STEMI patients in the Ottawa region with a pharmacoinvasive approach results in relatively low mortality. These results support the principle that a pharmacoinvasive strategy is feasible in a real-world setting and is associated with a favorable clinical outcome.

P-33
Identification of Vulnerable Aortic Plaque in Conventional FDG-PET Myocardial Viability
Yingwei Liu (Supervisor: Dr. Terrence Ruddy)

Purpose: ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been shown to be useful in identifying vulnerable plaque in major arteries. This study evaluated the feasibility of vulnerable plaque detection using routinely acquired cardiac FDG-PET viability studies in patients with severe coronary artery disease and left ventricular dysfunction.
Methods: Clinically indicated FDG-PET/computed tomography (CT) myocardial viability scans from 103 patients were retrospectively analyzed for FDG uptake in the proximal, ascending and descending thoracic aorta. PET emissions were co-registered with CT images based on extra-cardiac landmarks. Blood pool Standardized Uptake Value (SUV) of FDG uptake was determined from the lumen of the inferior vena cava. Plaque uptake was graded according to activity relative to blood pool using peak and mean target-to-background ratio (TBR): Grade 0 – $\leq$ 1, Grade 1 – 1.01-1.49; Grade 2 –1.5-1.99; and Grade 3 – $\geq$ 2. Two plaque quantifications method were used: the lesion region method and the aortic region method. Using the lesion region method, arterial plaque FDG uptake was quantified by drawing a region of interest around the individual lesions in the transaxial plane. Using the arterial region method, arterial plaque FDG uptake was quantified by drawing a ROI around the entire circumference of aorta in the transaxial plane.
Results: Of the 103 patients, 71 (68.9%) had a history of myocardial infarction, 88 (85.4%) were on statins, and 70 (68%) were on angiotensin-converting enzyme (ACE) inhibitors. Using the lesion region method, increased FDG uptake (mean TBR grade 1-3) was seen in 79/103 patients (77%), and grade 3 aortic uptake based on peak TBR was found in 12/103 patients (12%). Using the arterial region method, increased FDG uptake (mean TBR grade 1-3) was seen in 54/103 patients (52%), and grade 3 aortic uptake based on peak TBR was found in 9/103 patients (9%).
Conclusions: Detection of vulnerable atherosclerotic plaque in the aorta with conventional FDG viability scans is feasible. The rate of very positive uptake in this population of ischemic heart disease patients is low, possibly reflecting aggressive secondary risk factor modification including statin and ACE inhibitor use.

P-34
Kryptonite, a novel bone cement for primary sternal closure: mechanistic study using computerized tomography
S. Mastrobuoni (Supervisor: Dr. Marc Ruel)

Background: After conventional median sternotomy, functional recovery, wound healing, and prevention of infection are all influenced by early bone stability. Kryptonite is a novel bone cement that enables macro-adhesion and bony interdigitation due to material expansion after application to the sternal edges during closure. Although initial clinical experience has been reported, the mode of action of Kryptonite and the anatomic findings after the initial postoperative period remain unknown, and were evaluated in a blinded, randomized controlled setting.
Methods: Ten patients were evaluated. Kryptonite treated patients (n=5) included 3 males, with median age 67.0 years old (range 38-80), median BMI 33.3 (range 30.2-36.6), who underwent CABG surgery with use of bilateral internal thoracic arteries, and who received Kryptonite in addition to conventional sternal wire closure. They were compared to 5 controls with similar characteristics who did not receive Kryptonite. Patients were prospectively followed in order to evaluate the incidence of sternal wound complications, and underwent a high resolution computerized tomographic (CT) scan of the chest at 1 month postoperatively to assess anatomic findings.
Results: There were no perioperative complications. One patient in the Kryptonite group developed a deep sternal wound infection during follow-up. No dehiscence occurred in either group. In the Kryptonite group, CT scan revealed the presence of a gap (>1mm) in 4 patients, a step-off in 3, persistence of atelectasis in 5, and a pleural effusion in 2. Equivalent findings and frequency were noted in the control group (P = NS). None of the patients displayed bony union of the sternum at 1 month postoperatively.
Conclusion: Although Kryptonite appears to be safe and easy to use, blinded chest CT scans did not show any significant benefit on sternal healing. Larger studies are needed to further evaluate the clinical effectiveness of Kryptonite.

P-35
The prognostic value of change in RV function as measured on Radionuclide Ventriculography in patients with Heart Failure
Brian Mc Ardle (Supervisor: Dr. Lisa Mielniczuk)

Purpose: To evaluate the prognostic value of change in RV function as measured by gated-equilibrium Radionuclide Ventriculography (RNV) in patients with known cardiomyopathy.
Methods: We retrospectively analyzed the clinical records of patients with new- onset heart failure that attended our heart Function Clinic since January 2007 and included all patients who had undergone at least two RNV scans during the follow up period. Information on subsequent clinical events was obtained from patient records over the follow-up period.
RV and LV EF were measured semi-quantitatively on planar gated equilibrium RNV on an LAO projection to achieve optimal separation of heart chambers and change in both RV (ΔRVEF) and LV (ΔLVEF) function was measured as a percentage of the baseline

EF with a >10% increase or decrease relative to baseline being significant.
Using a Pearson's test we correlated ΔRVEF with ΔLVEF and also evaluated the prognostic value of ΔRVEF using a multivariate logistic regression model including Age, creatinine, and ΔLVEF for the composite outcome of; all cause mortality, heart transplant, and heart failure hospitalization.
Results: We included 118 patients for analysis (75% male, mean age 59 +/-27 years, 56% ischemic cardiomyopathy, mean follow-up 3.37 +/- 2.1 years, mean LVEF 31% +/-20, mean RVEF 30%+/-22). During the follow up period there were 23 events (6 deaths, 3 transplants and 14 heart failure admissions).
There was a statistically significant correlation between ΔRVEF and ΔLVEF (r= 0.43 p<0.0001). Univariate analysis of ΔRVEF showed a trend towards event prediction, with a positive ΔRVEF having an OR of; 0.297 ,95% Ci 0.076-1.159, p=0.08.
Both RVEF on follow-up RNV and ΔLVEF were significantly associated with events (p=0.001 and 0.006 respectively) on univariate analysis.
In those with severe RV dysfunction at baseline ΔRVEF was strongly predictive of events (p=0.04) and was superior to ΔLVEF on multivariate analysis.
Conclusion: In this study ΔRVEF in those with severe RV dysfunction at baseline and persistent RV dysfunction in the overall population were markers of poor prognosis independent of LV function. There was a trend for delta RVEF to also be related to outcomes, but this was not statistically significant.

P-36
Speckle Tracking: Effect of Age and Gender on Global and Regional Myocardial Strain

Chris Mykytyshyn (Supervisor: Dr. Terrence Ruddy and Dr. Kathy Ascah)

Purpose: Abnormal myocardial strain may be an early finding in myocardial disease processes. Speckle Tracking is a new ultrasound technique to measure myocardial strain from 2 dimensional echocardiographic images. The effect of gender and the aging process on myocardial strain is largely unknown. The purpose of the study was to establish the normal range for myocardial strains and determine whether gender or age affects myocardial strain.
Methods: 24 Men and women with no prior cardiac history underwent ultrasound examination using a Phillips ie33 equipped with an S-5 probe. Routine echocardiographic measurements of left ventricular systolic and diastolic function were made on the Xcelera system. Myocardial strains (global and regional longitudinal, circumferential and radial) were calculated off- line from raw image data using Q-lab Advanced Quantification. Patients with poor image quality or cardiac pathology on routine imaging were excluded from further analysis.
Results: There were 20 studies of adequate quality for further analysis: 10 males (mean age 46+ 18 yrs) and 10 females (mean age 57+19 yrs). The males had larger left atrial dimension (p=.045), LV end-diastolic dimension (p=.022) and thicker posterior walls (p= .029). There were no significant differences between the men and women in systolic or diastolic function (Biplane EF = 67.5 + 7.1% vs 69.8 + 8.4% p = .66). Mean global longitudinal strain was -14.97 + in males and -15.96 + 2.86 in females. (p= NS). Independent t-tests demonstrated no significant difference in regional longitudinal strain between males and females (p= .05/17 using Bonferroni correction) There was no significant correlation between age and myocardial strain. Males and females were then combined into a single group for analysis of regional strain by ANOVA. There were significant differences noted in the regional longitudinal mean strains: Basal LV -13.25+ 2.51, Mid-LV -16.20 + 2.61 and distal LV -19.21+ 3.19 (p = .004)
Conclusions: Initial analyses indicate that there are no gender or age related differences in regional or global myocardial strains. There is however a significant apex to base gradient in myocardial strain.

P-37
Measuring Coronary Artery Calcification using PET Computed Tomography Attenuation Correction Images

Ilias Mylonas (Supervisor: Dr. Benjamin Chow)

Purpose: We sought to understand the relationship between coronary artery calcium (CAC) measured using cardiac computed tomography (CT) and CAC using computed tomography attenuation correction (ACCT) images obtained during cardiac positron emission tomography (PET) perfusion imaging. CT measured coronary artery calcium (CAC-CT) is a well-validated and accurate tool for estimating atherosclerotic burden and prognosis. ACCT obtained during cardiac PET has been used to visually estimate CAC, however quantification using a non-gated ACCT images has not been described.
Methods: Patients with both CAC-CT and cardiac PET within 6 months of each other were identified. CAC-CT images were scored using the Agatston scoring method, while ACCT images were scored using different attenuation thresholds for calcium. CAC-CT and ACCT scores were compared.
Results: Between August 2007 and October 2010, 91 patients were included in the analysis. Interobsever reliability was excellent at all thresholds of detection tested. Pearson correlation was strongest between CAC-CT and ACCT at 50 HU threshold of detection (ACCT50). Implementing CAC categories (0, 1-100, 101-400, >400), there was a high degree of agreement between observers as well as between CAC-CT and ACCT50. Correlation was best for lower CAC scores however, as CAC-CT increased, ACCT50 was underestimated.
Conclusion: Quantifying CAC using ACCT images appears to be feasible and accurate. In a single cardiac PET examination, information regarding perfusion, LV function, flow quantification and CAC can be obtained without additional radiation.

P-38
Natural history and management of aortocoronary saphenous vein graft aneurysms: a systematic review of published cases

F. Daniel Ramirez (Supervisor: Dr. Edward R. O'Brien)

Purpose: Saphenous vein graft aneurysms (SVGAs) are a very rare complication of coronary artery bypass grafting (CABG). Our objective was to determine the clinical features and management options for aortocoronary SVGAs in an effort to develop an approach to identifying and managing patients with this complication.

Methods: We performed a systematic review of published cases in MEDLINE and SCOPUS between 1966 and December 2010. Standardized data were extracted by two independent reviewers. We identified 209 reported cases of aortocoronary SVGAs in 168 articles.
Results: Patients were predominantly male (86.6%) and had a mean age of 65.3 ± 10.6 years. SVGAs were identified on average 13.1 ± 6.0 years after CABG with a mean diameter of 60.7 ± 31.8 mm. Mechanical complications were reported in 34.0% of cases at presentation. Though most patients presented with chest pain (43.5%), SVGAs were commonly identified incidentally on imaging (35.4%). The most commonly employed investigations were cardiac catheterization (66.5%) and computed tomography (60.3%). In cases in which serial follow-up were described, the aneurysms continued to increase in size. Surgical management was reported in 58.4% of cases, percutaneous intervention in 15.8%, and conservative therapy in 20.1% with short-term mortality rates of 13.9%, 6.1%, and 23.8%, respectively.
Conclusions: SVGAs represent a rare but increasingly recognized complication of CABG most often seen remotely from the surgery. A large subset of patients with SVGAs are asymptomatic. It is hypothesized that the aneurysms continue to grow over time albeit at variable rates. Though further study is required, both surgical and percutaneous interventions appear to have favourable outcomes. In select patients, percutaneous management offers an alternative to repeat sternotomy.

P-39

Low-dose 3D PET Rubidium ARMI (Alternative Radiopharmaceutical for Myocardial Imaging): multicentre trial standards and quality assurance

Jennifer Renaud (Supervisor: Dr. Robert deKemp)

Purpose: The instability of Tc-99m supply requires alternative tracers for myocardial perfusion imaging (MPI). Rb-82 PET MPI has low radiation dose and may have superior accuracy, but requires further validation using 3D PET-CT. Rb-ARMI is a multicentre trial with an initial objective of standardizing Rb-82 PET MPI with highly repeatable interpretation in Canadian centers using 3D PET-CT technology.
Methods: Rest and stress phantom scans were conducted at all sites to standardize image reconstruction and quantitative scoring with 4DM-PET. Patients underwent low-dose (10 MBq/kg) rest and dipyridamole stress Rb-82 MPI. Sum stress, rest (SSS, SRS) and difference scores (SDS=SSS-SRS) were visually assessed using a 17-segment model. QA cases (n=25) from all sites were co-read to assess variability of scoring and overall interpretation. Cases with SDS differences ≥ 3 underwent a third review to reach consensus.
Results: Qualifying phantom scans resulted in the expected scores of SSS, SDS = 2 at all sites. Comparison of patient scores between core and recruiting sites showed very good agreement using the intraclass correlation coefficient (ICC): r = 0.91 for SSS and 0.86 for SDS. 81% of SSS scores and 87% of SDS scores had differences (site-core) ≤ 3. Most discrepancies occurred in large defects spanning multiple segments; however, these cases were all correctly interpreted as abnormal by recruiting and core sites. Following consensus review, overall agreement improved slightly to: r = 0.98 for SSS and 0.96 for SDS ($p < 0.05$ for both). Interpretation was found to be in excellent agreement with $\kappa = 0.93$. Image quality was perceived differently by the site vs. core reviewers (88% vs. 73% rated as good; $p< 0.05$).
Conclusions: With effective standardization and training, there was good agreement in scoring of Rb-82 MPI scans at the core and recruiting sites. Standardized and repeatable interpretation is achievable across imaging centers using different 3D PET-CT scanners.

P-40

Downstream utilization of cardiac investigations in coronary artery by pass patients: a comparison of anatomical versus functional index imaging with CT coronary angiography or cardiac SPECT.

Gary R Small (Supervisor: Dr. Benjamin Chow)

Background: Five years following coronary artery by pass surgery (CABG) prognosis deteriorates. Current guidelines for SPECT imaging indicate that investigation of these patients is appropriate even in the absence of symptoms. CT coronary angiography (CTA) with devices >/=64 detectors offers a valid alternative risk stratification approach.
Purpose: We sought to determine whether anatomical imaging with CTA or functional imaging with SPECT would generate more downstream investigations in CABG patients.
Methods: CABG patients were identified from a SPECT registry of 25,303 individuals and a CTA registry of 9060 individuals from studies performed from January 2006- December 2010 at the Ottawa Heart Institute. 1788 SPECT and 449 CTA patients were included in the analysis. Downstream utilization of stress echocardiography, invasive coronary angiogram (ICA), stress/ rest PET, CTA and SPECT were identified from patient records for the 6 months following index investigation. Patients who underwent a SPECT study after the initial CTA remained in the CTA cohort and were not included in the SPECT cohort and vice versa.
Results: Both groups had a similar prevalence of symptomatic patients (46% in the CTA group versus 50% of SPECT patients ($p=0.5$) and males (81% of SPECT and 78% of CTA patients). CTA patients were younger (66 versus 68 years old, $p=0.005$). In the CTA cohort 98 (22%) patients underwent downstream procedures versus 218 (12%) (+PET) following a SPECT equating to an absolute increase of 10% and a relative increase of 83% ($P<0.0001$). The increase was due to rise in the number of ICAs performed following CTA (10% of SPECT patients versus 17% of CTA patients $p<0.0001$).
Conclusions: Increased downstream utilization of tests occurred in CABG patients who underwent a CTA as their index study. This could not be explained by the prevalence of symptoms and was largely caused by an increase in the number of invasive angiograms. The increase in downstream utilization of invasive angiography following CTA may reflect a tendency of this technique to exaggerate the severity of a coronary lesion particularly in the presence of calcified coronary lesion, likely to be present in this population. Initial functional imaging with SPECT may help to prevent increases in downstream testing in the CABG population.

P-41

Incremental value of left ventricular function assessment on gated rest /stress dipyridamole technetium 99m SPECT imaging in the assessment of myocardial viability

Gary R Small (Supervisor: Dr. Robert Beanlands)

Background: Gated SPECT perfusion imaging is used in the evaluation of patients with ischemic cardiomyopathy to assess viability using resting perfusion and ischemia. The gated component of the scan assesses left ventricular function (LV) but is not used in the evaluation of viability. Changes in LV function on rest and stress imaging could indicate myocardial contractile reserve: measurement of which may contribute to viability assessment.
Purpose: We sought to determine whether measurement of contractile reserve would have incremental utility in the assessment of myocardial viability using rest/stress SPECT imaging.
Methods: From a SPECT registry of 25,303 patients, 34 individuals were identified who had ischemic cardiomyopathy (LVEF</= 35%, >/= 70% stenosis in >/=1 coronary artery) and had undergone an 18F-Flurodeoxyglucose (FDG) /perfusion PET scan within 6 months of the dipyridamole/ technetium ^{99m} tetrafosamin (Tc^{99m}) SPECT study. Ischemic segments (<70% tracer uptake on stress >/=10% improvement on rest) were declared viable and not used in wall motion analysis. Segments with persistent defects were analyzed for changes following stress in wall motion (using a 5 point scale) and wall thickness (>10% change). Segments with >/=50% FDG tracer uptake on FDG PET scanning were declared viable.
Results: 82% of patients were male. The average age was 66. 578 segments were analyzed, 286 (49%) were ischemic and not used for contractile reserve assessment. Of the remaining 292 segments which had persistent perfusion defects, 57 demonstrated a change in wall motion, 141 showed a change in wall thickness. Segments with a change in wall motion correlated with viability at PET (45/57 (79%) r=0.88 p<0.0001). Segments where wall thickness changed also correlated with PET findings (96/141 (68%) r=0.99 p<0.0001). The sensitivity and specificity of Tc^{99m} perfusion to detect viable myocardium was 61% and 85%. Sensitivity was increased by combining perfusion and regional wall motion (72%, p<0.05). Specificity was not (78%). Inclusion of wall thickness data did not improve the sensitivity or specificity of perfusion data findings. ROC analysis demonstrated no improvement in viability assessment with the inclusion of contractile reserve data.
Conclusion: Wall motion segmental change on stress/rest Tc 99m gated SPECT improved the sensitivity of perfusion alone to predict viable myocardium. The improved sensitivity of a SPECT model including perfusion and wall motion did not equate to an overall improvement on ROC analysis of the diagnostic performance of perfusion alone.

P-42

Comparison of a New Reconstruction Algorithm "Evolution software" to the Clinically used Filtered Backed Projection (FBP) for Myocardial Perfusion SPECT

Mohammed Qutub (Supervisor: Dr. Benjamin Chow)

Background: Myocardial perfusion scan (Tc-99m SPECT) is a well established method to diagnose ischemic heart disease. There are two currently used clinical reconstruction methods, first is called Filtered Backed Projection (FBP) and second is called iterative reconstruction. A common clinical issue that arises is equivocal studies. A newly developed reconstruction algorithm "EVOLUTION Software" (GE Healthcare) improves resolution and reduces noise in the reconstructed images. This software is used to improve image quality of short acquisition "half-time" and has never been investigated in long acquisition. Cardiac PET is the gold-standard modality for functional myocardial perfusion.
Objective: We compared images reconstructed with clinically used software and the new software, PET being a gold standard.
Methods: Retrospectively fourty-five patients (28 males, mean age is 59.1) underwent one day rest/stress Tc-99m Tetrofosmin (Myoview) ECG gated SPECT myocardial perfusion. All patients had equivocal studies defined as either undiagnostic SPECT or strong clinical suspicion of coronary artery disease despite normal SPECT and all patients had cardiac PET scans. Images were reconstructed with clinically used filtered backed projection (FBP) method and iterative reconstruction method with CT based attenuation correction (AC), as well as the new software with CT based attenuation correction (AC). The cases were anonymized and read by consensus by two experienced readers blindly. Clinical diagnosis was based on perfusion defects and wall motion abnormalities. The results of the studies were compared to the PET scans that were also anonymized.
Results: The new software with CT based AC changed the clinical diagnosis of 16 cases out of the 45. In 13 cases (29% of the total number of patients) the diagnosis was matching with the PET diagnosis. While in 3 cases (6% of the total number of patients) the diagnosis was different from the PET diagnosis. In the remaining 29 patients the diagnosis was unchanged amongst all different reconstruction algorithms compared to the PET diagnosis.
Conclusion: This new software could be helpful to more accurately diagnose equivocal cases or clinically discrepant cases. This can be useful in the clinical setting where there is no facility for cardiac PET. Further prospective studies are needed to define the role of this new software.

ALLIED AND POPULATION HEALTH POSTER PRESENTATIONS

P-43

Extending Tobacco Treatment Excellence (ExTENDS): A Quantitative Evaluation of a National Dissemination of Systems

Laura Jones (Supervisor: Kerri-Anne Mullen)

Background: The Ottawa Model for Smoking Cessation (OMSC) is an evidence-based clinical smoking cessation program that uses the "5 A's" approach to cessation (ask, advise, assess, assist and arrange). The ExTENDS project was focused in the area of cessation and on the priorities of mobilization of networks and increased use of existing services and programs, knowledge transfer, and increasing the availability and use of smoking cessation medications. The purpose of this evaluation was to examine the impact of the ExTENDS project on OMSC program reach and efficacy among patients seen in outpatient clinical settings.
Methods: A quantitative evaluation was conducted in 32 outpatient clinical settings (20 primary care clinics and 12 specialty clinics) that

implemented the OMSC program during the ExTENDS project period (between November 2009 and March 2011) in health regions in British Columbia, New Brunswick, and Ontario. Baseline comparisons of patient characteristics were performed using univariate analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Chi-square tests were used to compare 7-day point prevalence and 1-month continuous quit rates at 1, 3, and 6 months.
Results: Of the 32 implementing sites, a total of 4287 smokers received a smoking cessation consultation. Of the 4287 smokers reached by the OMSC program, 84.7% (3630 smokers) agreed to be enrolled in the 6-month automated follow-up system. Across sites, the ExTENDS project was effective at increasing smoking cessation rates among patients. The 7-day point prevalence abstinence rate was 38.6% at one month, 31.4% at 3 months, and 21.4% at 6 months. Forty-one percent of patients who were smoke-free at one month were abstinent at 6 months.
Discussion/Conclusion: Much has been accomplished in the area of clinical smoking cessation through OMSC initiatives and additionally with the ExTENDS project reaching over 4000 smokers. Outpatient clinics serve as an opportune venue to address smoking cessation with a captive audience - that is, in a setting that makes it possible for smokers to receive smoking cessation advice and medications from a health care professional.

P-44
Learning Effect in 6-Minute Walk Testing Among Low Intensity Cardiac Rehabilitation Participants: A Pilot Study

Marja-Leena Keast

Background: Six-minute walk test (6MWT) has been used in our low intensity cardiac rehabilitation (CR) program at the University of Ottawa Heart Institute's Minto Prevention and Rehabilitation Centre since 2006. 6MWT was adopted instead of peak VO_2 exercise stress testing as it is better tolerated by elderly, low intensity CR participants. Results of the 6MWT are used for initial and final exercise prescription, and as an outcome measure for functional capacity.
Objectives: The purpose of the present research was to evaluate the degree of learning effect in 6MWTs at baseline and after 12 weeks among participants in our on-site, low intensity CR program. We also assessed the actual treatment effect post-program.
Methods: A total of 62 participants (50% male; mean age 69.7 yrs ± 9.5) enrolled in the low intensity CR program were recruited into the study. Two 6MWTs (walk 1, walk 2) were performed at baseline and two 6MWTs (walk 3, walk 4) at 12 weeks. The walking distance between walks 1,2 and walks 3,4 were compared to detect any learning effect pre- and post-program. Learning effects and METs at baseline and 12 weeks were also compared. To account for any sex differences, men and women were analyzed separately. Paired *t*-test was applied for the analysis.
Results: Overall, participants walked a greater average distance at 12 weeks compared to baseline (447 m ± 92 vs. 404 m ± 91; $p<0.001$). A significant learning effect was observed for both men and women during baseline 6MWTs. For the 12-week 6MWTs, men alone had a significant learning effect. When comparing baseline and 12-week learning effects, only women demonstrated a significantly higher learning effect at baseline than at 12 weeks (15 m ± 35 vs. -4 m ± 30; $p=0.037$), although learning effect for men was also higher at baseline than at 12 weeks (23 m ± 28 vs. 12 m ± 31; $p=0.066$). Average METs significantly increased after 12 weeks in the entire sample (3.13 METs ± 0.43 vs. 2.90 METs ± 0.44; $p<0.001$), and for men and women separately.
Conclusions: Participation in a 12-week low intensity CR program significantly improved METs level. This finding confirms our belief that the 6MWT is a valid functional capacity assessment tool in the low intensity CR population. Our results also underscore the importance of conducting a practice 6MWT at program entry since baseline learning effect was higher than the learning effect at 12 weeks.

P-45
Pilot study of a screening and intervention program for diabetes among hospital patients: the Ottawa Model for Undiagnosed Diabetes

Jana Kocourek (Supervisor: Dr. Robert Reid)

Background: Systematic screening of hospitalized patients for hyperglycemia may allow previously unrecognized cases of diabetes mellitus (DM) to be identified and connected to community care. We conducted an observational study in patients presenting to hospital for coronary artery disease (CAD) and orthopedic surgery to assess the feasibility of a systematic screening and intervention protocol for hyperglycemia to identify new cases of DM.
Methods: Three hundred and fifty four consecutive, consenting patients without known DM underwent baseline blood testing and were classified as diabetes unlikely or possible diabetes on the basis of HbA1C and random or fasting blood glucose levels. Attending physicians, patients, and the patient's primary care provider were informed of all 'possible diabetes' classifications. Patients with possible diabetes were asked to return to the study centre 6 weeks after hospitalization for confirmatory 2h oral glucose tolerance testing (2h OGTT). Levels of eligibility, consent, adherence and protocol completion were used as indicators of program feasibility. The primary outcome was the number of new cases of DM confirmed by 2h OGTT, 6 weeks after hospital discharge.
Results: Among 2288 patients with CAD, 659 were eligible for screening (28.8% of those assessed), 224 consented (34.0% of those eligible), 14 were classified as DM possible (6.3% of those consenting), and 9 (75.0% of those with possible diabetes) completed the 2h OGTT. Among 188 patients undergoing orthopedic surgery, 136 were eligible for screening (72.3% of those assessed), 130 consented (95.5% of those eligible), 10 were classified as DM possible (7.6% of those consenting), and 8 (80.0% of those with possible diabetes) completed the 2h OGTT. Of the 17 OGTT tests completed 6 weeks after hospitalization, DM was confirmed in 11 patients (65%) and impaired glucose tolerance was confirmed in 6 patients (35%). All confirmed cases of DM were under the care of their primary care provider within 6 weeks of hospital discharge.
Conclusions: Systematic screening for hyperglycemia among 354 hospitalized patients yielded 11 confirmed cases of DM (3.1% of those screened) and 6 cases of impaired glucose tolerance (1.6% of those screened). The screening protocol is more feasible to apply in patients presenting for orthopedic surgery compared to patients presenting with CAD, primarily because more orthopedic patients are eligible for screening. It may be feasible to evaluate the protocol in patients presenting to hospital for orthopedic surgery in multiple sites.

P-46

Extending Tobacco Treatment Excellence (ExTends): A Qualitative Evaluation of Factors Relating to Program Sustainability

Jana Kocourek (Supervisor: Kerri-Anne Mullen)

Background: The Ottawa Model for Smoking Cessation (OMSC) is an evidence-based intervention program for smoking cessation in clinical settings. The *Extending Tobacco Treatment Excellence: A National Dissemination of Systems* (ExTENDS) project was an initiative designed to expand the OMSC across a spectrum of clinical environments, mainly outpatient clinical settings. The purpose of this evaluation was to examine the impact of the ExTENDS project on factors related to the sustainability of the OMSC program.
Methods: A qualitative evaluation was completed to examine relevant factors at the healthcare provider, organizational, and health authority levels related to program sustainability according to the Shediac-Rizkallah & Bone (1998) model: (1) program design and implementation factors (i.e. OMSC introduction and implementation); (2) factors within the organizational setting (i.e. clinical sites); and (3) factors in the broader system environment (i.e. regional health authority). Forty five semi-structured telephone interviews were conducted with representation from clinicians delivering the ExTENDS intervention (as per OMSC), administrative managers at participating ExTENDS sites, and key health authority officials.
Results: The following factors were identified as key components to program sustainability: **(1)** Program design and implementation factors: Duration of external support, sustainability or transition plan, regional partnerships, and free smoking cessation medication (Smart Cards), **(2)** Factors within the organizational setting: Designated smoking cessation coordinator or champion, and reliance on external support, **(3)** Factors in the broader system environment: Collaborative relationships with provincial and regional tobacco cessation programs.
Discussion/Conclusion: The process of program sustainability has the potential to be facilitated if all identified factors were considered and if service providers adopted the smoking cessation intervention program as a standard of care.

P-47

What resources exist for health care providers to address smoking cessation among pregnant women, and what factors need to be considered for future intervention strategies in the Baffin Region of Nunavut?

Chantal Nelson (Supervisor: Dr. Robert Reid)

Background: This study investigated the perspectives of health care providers on barriers and facilitators of smoking cessation for pregnant women in the North and to examine what smoking cessation resources are available for health care providers in the Baffin Region.
Methods: This was a qualitative study using a structured interview. The study took place in two, 3-week recruitment periods, between October 2008 and October 2010 in 13 communities in the Qikiqtaaluk region of Nunavut.
Results: 83.3%, of the health care providers (HCP) asked pregnant women about their smoking status; 75.0% assessed readiness to quit smoking and 66.7% advised their pregnant patients to quit smoking. HCP who did not advise women to quit was because: HCP felt women knew and understood the harms of smoking; providing education on the effects of smoking was more effective than advising them to quit; and the context of the patient encounter did not permit this discussion. With the exception of the posters, no smoking cessation resources were identified for pregnant women.
Discussion/Conclusion: Most of the health care providers in this sample felt that addressing smoking cessation among pregnant women in the North was necessary as the extended networks of smokers provide ample opportunity for pregnant women to continue smoking, be exposed to smoke or relapse into smoking if she succeeds in quitting. The current approach used by health care providers to address smoking cessation with their patients ranged considerably, from no approach, guilt tactics, and supportive dialogue. A more unified strategy may be needed in the Baffin Region.

P-48

A qualitative exploration of physical activity patterns among family members of people with coronary heart disease

Dana Riley (Supervisor: Dr. Robert Reid)

Introduction: Physical inactivity is a well-known risk factor for coronary heart disease (CHD). Targeted interventions aimed at family members of those with established CHD may be an effective way to identify individuals at high risk and link them to effective risk factor modification. The objective of the current study was to investigate, using a family systems perspective, the role of recent hospitalization of a spouse or parent for CHD in activating family members to engage in physical activity (PA).
Methodology: A qualitative research design was employed involving semi-structured interviews to elicit perceptions of the factors in the social and physical environment that influence PA. Interviews were audiotaped, transcribed, coded and analyzed, which involved inductively documenting emerging themes.
Findings: Interviews were conducted with 36 participants; 17 spouses and 19 offspring. Spouses were more likely to provide care and support and to engage in PA with their spouse after the CHD event. Many spouses expressed that their own PA was limited by the capabilities of their partner. Offspring expressed an increased perception of their own future risk of CHD, citing genetics as a prominent concern; however, this did not necessarily translate into PA behaviour change.
Conclusion: There are fundamental differences in how spouses and offspring engage in PA and how they adapt their PA following a CHD event in a family member. The data suggests awareness of an increased susceptibility to CHD is not stimulating participants to increase their own PA to prevent future risk, particularly among offspring, but they may take other actions. Spouses are more likely to engage in PA with the CHD patient than offspring, suggesting this shared environment can promote PA, although intensity may be limited. Family members may need additional interventions to translate their perceived future risk of CHD into current PA behaviour change.

P-49

Effects of a 12-week behavioural risk reduction program on physical activity levels in family members of patients with coronary heart disease: Secondary outcomes from a randomized controlled trial

Dana Riley (Supervisor: Dr. Robert Reid)

Background: Interventions to increase moderate-vigorous physical activity (MVPA) among family members of patients with coronary heart disease are needed.
Purpose: To determine whether a 12-week behavioural risk reduction intervention caused self-reported MVPA to increase and to identify the associated Theory of Planned Behaviour (TPB) constructs.
Methods: Three hundred twenty-four physically inactive (<150 minutes/week MVPA) participants were enrolled in a randomized controlled trial. The main outcome was achievement of guideline recommended levels of MVPA (≥150 minutes/week) at 12-weeks. Groups were compared using logistic regression. TPB constructs were examined using t-tests and Spearman rank correlations.
Results: Intervention participants were significantly more likely to meet MVPA guidelines at 12-weeks (OR=3.54, 95% CI 2.22-5.63, p<.001). The outcome was significantly correlated with increases in control belief, behavioural belief, subjective norm, attitude, perceived behavioural control and intention (all p<.01) among intervention participants and attitude (p<.01) and intention (p<.01) among controls.
Conclusion: The intervention caused self-reported MVPA to increase; this was significantly correlated with greater increases in TPB constructs among intervention participants.

P-50

Neighbourhood walkability and physical activity among family members of people with heart disease who participated in a randomized controlled trial of a behavioural risk reduction intervention

Dana Riley (Supervisor: Dr. Robert Reid)

This study adds to the current literature investigating the relationship between individuals' physical activity (PA) and the built environment. Self-reported PA from a prospective behavioural risk reduction intervention was explored in the context of objectively measured Walk Scores and neighbourhood walkability in Ottawa, Canada.
It was hypothesized that (i) participants living in high walkability neighbourhoods would be more likely to meet the PA guidelines at baseline compared to participants living in low walkability neighbourhoods and (ii) walkability would interact with the intervention arm (FRR vs. SC), with participants allocated to the intervention and living in the highest walkability neighbourhoods having the highest odds of achieving the PA target (≥ 150 minutes MVPA/week) at 12-weeks.
Participants in the intervention arm had significantly higher odds of meeting PA guidelines at 12-weeks compared to the standard care control group. This was not influenced by Walk Scores or walkability. This individual-level intervention was effective in assisting participants to overcome potential structural barriers presented by their neighbourhood to meet PA guidelines at 12-weeks.

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