Research DAY 2017

Department of Medicine

Thursday May 25, 2017

ORAL PRESENTATIONS

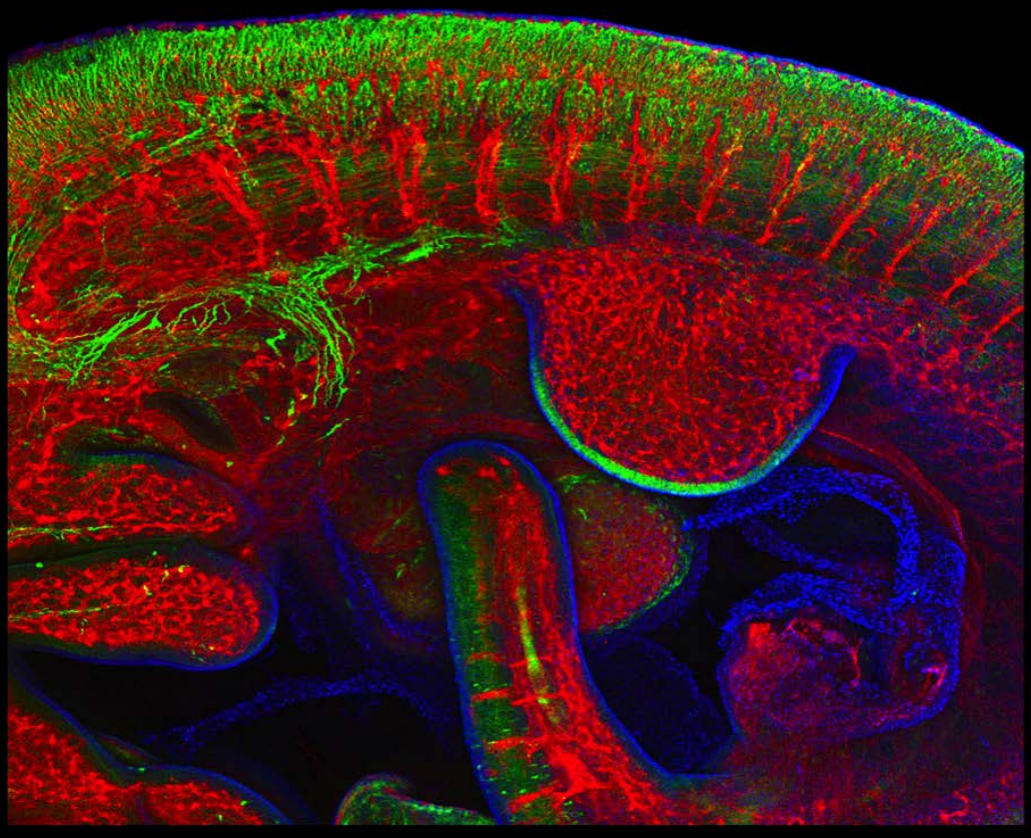
Classroom D, WMC 2F1.04

8:00 a.m. – 5:00 p.m.

POSTER PRESENTATIONS

Lower Level John W. Scott Health Sciences Library

All Day Viewing



Graduate Students | Residents | Postdoctoral Fellows

Research DAY 2017
Department of Medicine

In 2016, members of the Department of Medicine contributed 702 peer-reviewed research papers to the literature, plus many scholarly reviews, book chapters, books and abstracts. The work spans the spectrum from molecule to patient and from patient to health systems. Research is central to what we do – it is the life-blood of medicine.

With some help from their supervisors, most of the Department's research work is actually done by residents, graduate students and postdoctoral fellows – and this work is showcased today. The Department of Medicine graduate program is one of the largest at this University with 99 graduate students and 30 postdoctoral fellows. Also, over 300 residents are training in our core specialty and subspecialty programs. Almost all of the trainees are involved in research at some level.

The trainees who are presenting the work today have put a lot of effort into their presentations, and many of them will take their findings to national and international conferences. You can help them by showing how much you value their effort, you can get a preview of what will be published by this Department in the near future, and by chatting with the presenters, you can add your ideas to this ongoing research. As is the case every year, the oral abstracts will be presented in Classroom D, and posters will be shown in the lower level of the John W. Scott Library (lunch is served). This year, I would like to welcome two guest adjudicators for the oral presentations:

Mark Nicolls, MD, Chief, Division of Pulmonary & Critical Care Medicine at Stanford University School of Medicine.

Michael Mengel, MD, Chair of the Department of Laboratory Medicine and Pathology at the University of Alberta.

Barbara J. Ballermann, MD

Evangelos D. Michelakis, MD
Associate Chair (Research)

Two poems by C.P. Cavafy (in lieu of comments)

1. The Satrapy

Too bad that, cut out as you are
for grand and noble acts,
this unfair fate of yours
never offers encouragement, always denies you success;
that cheap habits get in your way,
pettiness, or indifference.
And how terrible the day you give in
(the day you let go and give in)
and take the road for Susa
and go to King Artaxerxes,
who, well-disposed, gives you a place at his court
and offers you satrapies and things like that—
things you don't want at all,
though, in despair, you accept them just the same.
You long for something else, ache for other things:
praise from the Demos and the Sophists,
that hard-won, that priceless acclaim—
the Agora, the Theatre, the Crowns of Laurel.
You can't get any of these from Artaxerxes,
you'll never find any of these in the satrapy,
and without them, what kind of life will you live?

2. Waiting for the Barbarians

What are we waiting for, assembled in the forum?

The barbarians are due here today.

Why isn't anything happening in the senate?
Why do the senators sit there without legislating?

Because the barbarians are coming today.
What laws can the senators make now?
Once the barbarians are here, they'll do the legislating.

Why did our emperor get up so early,
and why is he sitting at the city's main gate
on his throne, in state, wearing the crown?

Because the barbarians are coming today
and the emperor is waiting to receive their leader.
He has even prepared a scroll to give him,
replete with titles, with imposing names.

Why have our two consuls and praetors come out today
wearing their embroidered, their scarlet togas?
Why have they put on bracelets with so many amethysts,
and rings sparkling with magnificent emeralds?
Why are they carrying elegant canes beautifully worked in silver and gold?

Because the barbarians are coming today
and things like that dazzle the barbarians.

Why don't our distinguished orators come forward as usual
to make their speeches, say what they have to say?

Because the barbarians are coming today
and they're bored by rhetoric and public speaking.

Why this sudden restlessness, this confusion?
(How serious people's faces have become.)
Why are the streets and squares emptying so rapidly,
everyone going home so lost in thought?

Because night has fallen and the barbarians have not come.
And some who have just returned from the border say
there are no barbarians any longer.

And now, what's going to happen to us without barbarians?
They were, those people, a kind of solution.

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Research Day Guest Oral Adjudicator

Dr. Mark Nicolls

Dr. Nicolls is a Professor in the Department of Medicine and Chief of the Division of Pulmonary and Critical Care Medicine. He is also a member of the Stanford Institute of Immunity, Transplantation and Immunology. He has a joint appointment with Immunology and Rheumatology and is Director of the Lung Immunology Program at Stanford. He has trained a number of post-doctoral fellows now in Academic careers. He has active funding support from a P01 and R01 grants. Additionally, he leads an NIH-funded multicenter trial focused on B cell depletion for the treatment of systemic sclerosis-associated pulmonary hypertension. He also help lead, with Marlene Rabinovitch and Mike Snyder at Stanford, a K12 training grant focused on the utilization of omic technologies to study pulmonary vascular disease. His lab works on transplantation immunology (especially as it pertains to airways and lungs) and pulmonary hypertension. He uses a combination of transplantation, lineage fate mapping and biomonitoring techniques to assess the changes that occur as allografts progress towards chronic rejection. He has >20 years of experience working in immunology-related research, creating the first non-lytic anti-CD3 monoclonal antibody as a tolerizing immunotherapy as a Stanford Medical Student. His most recent projects focus on the role of leukotriene B4 (LTB4) in the evolution of pulmonary hypertension and lymphedema and why preserving microvascular health may prevent chronic rejection in solid organ transplant recipients. He recently helped develop two clinical trials based on their pulmonary hypertension and lymphedema research that are now enrolling (LIBERTY and ULTRA, respectively).

Research Day Guest Oral Adjudicator

Dr. Michael Mengel

Dr. Mengel is Chair of the Department for Laboratory Medicine and Pathology at the University of Alberta, Edmonton, Canada. He is an Anatomical Pathologist sub-specialized in Transplantation and Renal Pathology at the Division of Anatomical Pathology, University of Alberta Hospital. Outside his faculty Dr. Mengel is engaged in various international sub-specialty societies related to nephropathology and organ transplantation: past Chair Transplant Diagnostics Community of Practice in the American Society of Transplantation; Board member International Banff Foundation for Allograft Pathology; Board member Canadian Society of Transplantation; Board member of the International Renal Pathology Society.

He studied medicine at the Semmelweiss University in Budapest, Hungary before going on to specialise in pathology and further in transplantation pathology and nephropathology. Before moving to Edmonton he was head of the transplant pathology service at the Hannover Medical School, Germany. Dr. Mengel has published widely in the field of organ transplantation and his current work is focused on applying molecular techniques to biopsy specimens, with the aim to increase diagnostic precision in organ transplantation.

Meeting at a Glance

8:00 – 8:10	Welcome Address *Dr. Evangelos Michelakis, Associate Chair, Research* *Dr. Barbara Ballermann, Chair*
8:10 – 8:30	**Keynote Speaker** *Dr. Mark Nicolls*
8:30 – 9:45	Oral Presentations
9:45 – 10:00	**Break**
10:00 – 11:15	Oral Presentations
11:00 – 1:00	Poster Presentations and **Lunch**
1:00 – 1:15	Translational Fellowship Award Presentation
1:15 – 2:30	Oral Presentations
2:30 – 2:45	**Break**
2:45 – 4:00	Oral Presentations
4:00	**Award Ceremony**

Scoring Criteria

Oral & Poster Prsentations
(1=Poor, 5= Excellent)

Clarity and Justification of the Research Questions/Hypothesis	1 2 3 4 5
Appropriateness of the Methods Used to Answer the Questions/Hypothesis	1 2 3 4 5
Validity and Relevance of the Results to the Questions/Hypothesis	1 2 3 4 5
Quality of the Discussion and Conclusion	1 2 3 4 5
Visual Layout and Visual Impact	1 2 3 4 5
Oral Response to Adjudicator's Question	1 2 3 4 5
TOTAL SCORE	_____ **35**

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9:00	**Sotirios Zervopoulos** Supervisor: Evangelos Michelakis	GS	Lamin A forms a structural platform for protein-protein interactions of histone modifying and metabolic enzymes: a novel link between metabolism and epigenetics	29
9:15	**Vivek Gandhi** Supervisor: Harissios Vliagoftis	GS	INSULIN REGULATES PROTEINASE-ACTIVATED RECEPTOR-2 EXPRESSION ON AIRWAY EPITHELIUM	30
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4:00 **Award Ceremony (Bernard Snell Hall – Upper Foyer)**

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Association Between Epicardial Adipose Tissue And Cardiovascular Outcome In Non-cardiac Surgery

Lingyu Xu 1,2 ; Craig Butler 1; on behalf of the CTA VISION investigators.
Supervisor: Dr. Ian Paterson

INTRODUCTION

Worldwide 200 million adult patients undergo major noncardiac surgery, 5 million of whom suffer a major vascular complication. Epicardial adipose tissue (EAT), defined as the adipose tissue between myocardium and visceral pericardium, is active vasocrine and paracrine organ that can affect myocardium and coronary arteries. We hypothesize that EAT may predict perioperative cardiovascular adverse outcome among patients undergoing major noncardiac surgery.

METHODS

76 patients from Edmonton site of Coronary CTA VISION Study with a broad spectrum of vascular diseases undergoing elective noncardiac surgery prospectively underwent a preoperative cardiac CT scan. EAT volume was estimated using a semi-automated 3D Fat volume application (Tera-recon). We used hounsfield threshold of -190U to -30U on non-contrast coronary artery calcium score datasets. The primary outcome was non-fatal myocardial infarction and cardiovascular mortality post-surgical 30 days.

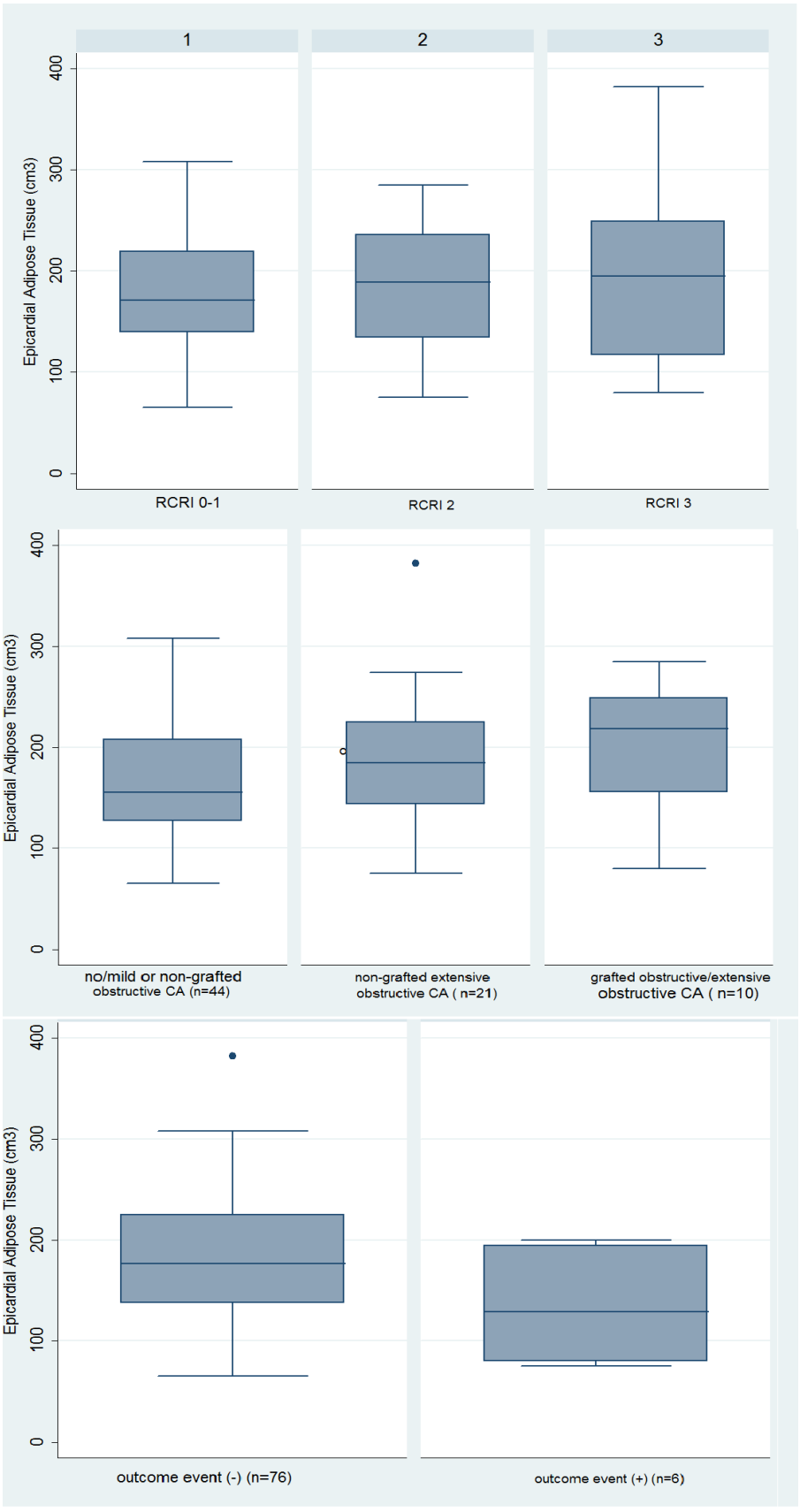
RESULTS

EAT volume increases with increased revised cardiac risk index (RCRI, 173.1±55.8 cm3 (RCRI 0-1) vs 193.2±77.9 cm3 (RCRI 2) vs 204.6 ± 119.1 cm3 (RCRI 3), P = 0.3727) and increased coronary stenoses (172.3±68.7 cm3 (no/mild-non-grafted obstructive coronary stenoses) vs 187.9±68.3 cm3 (non-grafted extensive obstructive coronary stenoses) vs 200.3±64.6 cm3 (grafted obstructive/extensive obstructive coronary stenoses), P = 0.4253), but was not statistically significant; During a follow-up of 30 days, 6/76 (7.9%) had an outcome event. Patients with outcome events had a lower volume of EAT (180±62 cm3 (Outcome Event (-)) vs 134±56 cm3 (Outcome Event (+), P = 0.0855). An optimal EAT cutoff was derived from Receiver operator characteristic methods. Patients with EAT≤102 cm3 had significantly worse perioperative outcome (Hazard Ratio (HR) = 6.68, Log-rank P = 0.0070), compared to patients with EAT >102 cm3.

CONCLUSIONS

Increasing EAT volume does not confer increased risk of cardiovascular events following non-cardiovascular surgery despite positive correlation with RCRI and severity of coronary stenoses.

Supervisor: Dr. Ian Paterson


1
2
3
Epicardial Adipose Tissue (cm3)
0
100
200
300
400
RCRI 0-1
RCRI 2
RCRI 3
Epicardial Adipose Tissue (cm3)
0
100
200
300
400
no/mild or non-grafted
obstructive CA (n=44)
non-grafted extensive
obstructive CA (n=21)
grafted obstructive/extensive
obstructive CA (n=10)
Epicardial Adipose Tissue (cm3)
0
100
200
300
400
outcome event (-) (n=76)
outcome event (+) (n=6)

Adherence to an anti-inflammatory diet prevents increases in colonic inflammation in ulcerative colitis patients in remission

Ammar Hassanzadeh Keshteli, Karen Madsen, Cheryl Nickurak, Karen Kroeker, Rupasri Mandal, David Wishart, Rosica Valcheva, Sander van Zanten, Branden Halloran, Richard Fedorak, Levinus Dieleman
Supervisor: Dr. Karen Madsen, Dr. Levinus Dieleman

INTRODUCTION

Epidemiological studies suggest a relationship between ulcerative colitis(UC) and diet, though data from randomized controlled trials(RCTs) in this area is lacking.Here we investigate the effectiveness of an anti-inflammatory diet for maintenance of remission in UC.

METHODS

In this 6-month RCT, adult UC patients in clinical remission who had a disease relapse within the previous 18 months were randomized to either an “Anti-inflammatory Diet” or “Canada’s Food Guide”. Dietary recommendations were provided in four face-to-face(baseline,month 1,3,6) and three telephone (month 2, 4, 5) sessions. Meal plans provided to patients in the anti-inflammatory diet group contained high levels of fiber, prebiotics, anti-oxidants, probiotics, and omega-3 fatty acids. These subjects were instructed to decrease their intake of red meat, sugar and alcohol. Partial Mayo scoring was done monthly to assess clinical relapse. At baseline, month 1,3 and 6(or relapse), fecal calprotectin (FCP,an indicator of colonic inflammation), serum CRP, and quality of life (using the Short Inflammatory Bowel Disease Questionnaire) were assessed. Metabolomic assessment using nuclear magnetic resonance (NMR) spectroscopy was performed on serum taken at baseline and month 6(or relapse).

RESULTS

Fifty-three subjects were randomized. Mean age was 41.4±14.7y and 34(64.2%) were female. Eight (30.8%) subjects in the anti-inflammatory and 9 (33.3%) in the control group relapsed(P=1.0). FCP over the study period was increased significantly in those following Canada’s Food Guide while those following the anti-inflammatory diet showed no increase in FCP(Figure1). At baseline, metabolomic profiles were similar between the two groups, but after 6 months of dietary intervention the metabolomic fingerprints shifted significantly(Figure 2). Glycerol,acetoacetate, pyruvic acid and valine were significantly shifted. CRP and quality of life scores were unchanged in each group.

CONCLUSIONS

Modification of diet towards an inclusion of anti-inflammatory and reduction of inflammatory food-types can prevent FCP increases in UC patients. In addition, dietary modification alters specific metabolites related to energy metabolism.

Supervisor: Dr. Karen Madsen, Dr. Levinus Dieleman

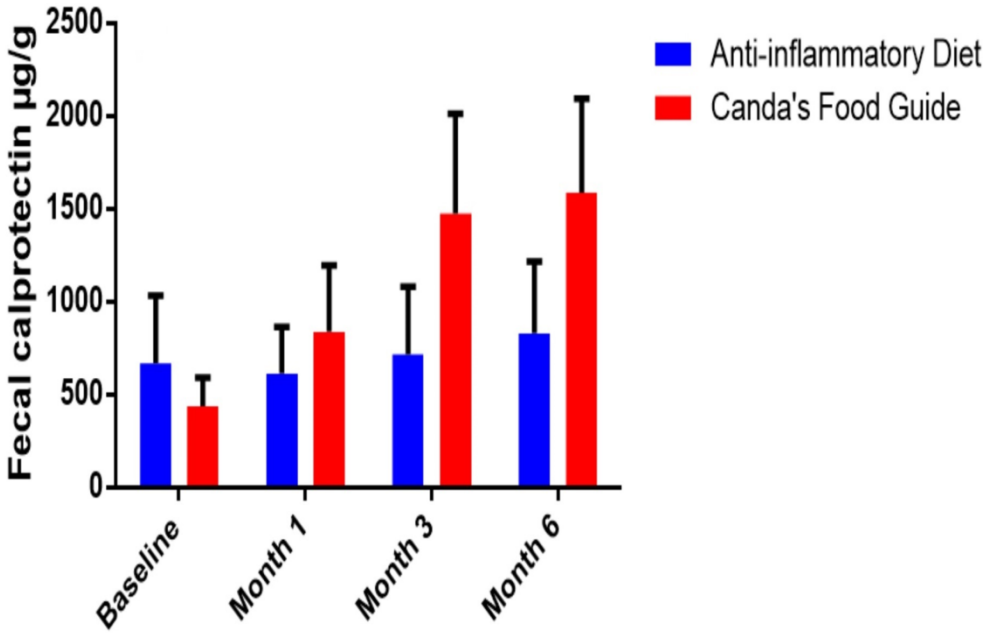


Figure 1. Changes in fecal calprotectin levels in ulcerative colitis patients randomized to the two diet groups. While there was a significant increase in FCP from baseline to month 6 in patients randomized to Canada's Food Guide diet, FCP did not change significantly from baseline to month 6 in subjects randomized to Anti-inflammatory diet group (P=0.02, repeated measures ANOVA for comparison of changes between the two diet groups).

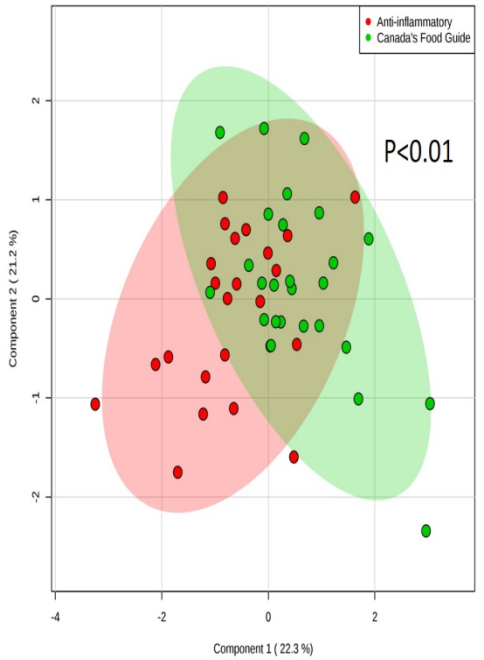


Figure 2. Partial least squares discriminant analysis plot showing discrimination of ulcerative colitis patients in the two diet groups based on their serum metabolomic profiles at month 6 or the time of disease relapse.

Lamin A forms a structural platform for protein-protein interactions of histone modifying and metabolic enzymes: a novel link between metabolism and epigenetics

Zervopoulos SD, Haromy A, Garic B, Stenson T, Sutendra G and Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Lamins form a mesh spreading throughout the nucleus, binding to DNA and histone-modifying enzymes, providing structural integrity. They also form deep intranuclear invaginations with unknown function. Lamin A binds to the histone deacetylase sirtuin 6 (SIRT6) but the role of this is unclear. Recently, p300 (a histone acetyltransferase) was found in complex with two metabolic enzymes that "moonlight" in the nucleus promoting acetyl-CoA production: pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase complex (PDC). We hypothesized that lamin A provides a structural platform for histone-modifying and metabolic enzymes, facilitating interaction and optimizing histone acetylation in defined microdomains.

METHODS

We exposed several cell lines (A549 lung cancer, small-airway epithelial, 786-O renal cancer, and proximal tubule cells) to stimuli promoting metabolic enzyme entry to the nucleus or cell cycle progression, PDC and lamin siRNA; and used high-resolution confocal microscopy, immunoblots and co-immunoprecipitation.

RESULTS

Cancer cells have more nuclear invaginations than their healthy controls. Dynamic 3D reconstruction showed that lamin A (in both invaginations and nucleosome) is spatially closely associated to DNA, PDC, PKM2, SIRT6, p300 and acetyl-histone 3. Immunoprecipitation revealed lamin A and PDC interaction. Synchronized cells showed a dynamic and similar distribution pattern of lamin and PDC throughout the cell cycle; maximal overlap occurred upon S phase entry and was associated with increased p-Rb levels. Knockdown of lamin A decreased nuclear PDC without affecting total PDC levels, suggesting that lamin is essential for nuclear entry and/or retention of PDC.

CONCLUSIONS

Lamin A may provide a structural platform facilitating the formation of functional protein units, like those involved in histone acetylation. This may be critical for entry and/or retention of enzymes (like PDC) that optimize histone acetylation. Cancer cells have more lamin invaginations than their healthy controls, suggesting a unique nuclear remodeling. While invaginations increase the surface area for functional protein interactions, their role remains unknown.

Supervisor: Dr. Evangelos Michelakis

INSULIN REGULATES PROTEINASE-ACTIVATED RECEPTOR-2 EXPRESSION ON AIRWAY EPITHELIUM

Vivek Gandhi1*, Jean Buteau2 and Harissios Vliagoftis1
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Proteinase-Activated Receptor-2 (PAR-2), a receptor for aeroallergens and endogenous serine proteinases, has been implicated in the pathophysiology of allergic airway inflammation. PAR-2 is upregulated in the airway epithelium of asthmatic individuals, but the factors responsible and the consequences of increased expression are unknown. We hypothesize that cellular stress present in inflamed airways regulates PAR-2 expression on airway epithelium.

METHODS

Normal Human Bronchial Epithelial (NHBE) cells were grown in a serum free media in the presence or absence of bovine pituitary extract, epidermal growth factor and insulin. PAR-2 expression (qRT-PCR, confocal microscopy) and function (PAR-2-mediated calcium flux) were studied.

RESULTS

Growth factor deprivation upregulated PAR-2 mRNA and protein; this upregulation was exclusive due to insulin deprivation. Addition of insulin reversed PAR-2 upregulation in both insulin deprived and growth factor deprived cells. PAR-2-mediated calcium flux was higher in insulin-deprived cells compared to cells grown in the presence of insulin, linking increased PAR-2 expression with increased PAR-2 function. Phosphoinositide 3-kinase (PI3K) inhibition partially abolished the regulatory effect of insulin on PAR-2 expression. Insulin negatively regulates the function of FOXO-1 transcription factor by inducing nuclear exclusion of FOXO-1. Expression of constitutively active FOXO-1 resulted in increased PAR-2 expression in the presence of insulin, and inhibition of FOXO-1 prevented insulin deprivation-induced PAR-2 upregulation. Finally, we found that obese overfed mice had lower PAR-2 expression in lungs. We hypothesize that this decreased PAR-2 expression is the result of increased insulin levels in obese overfed mice indicating that the change in insulin levels could alter PAR-2 expression in lungs in vivo.

CONCLUSIONS

Insulin may play an anti-inflammatory role by controlling PAR-2 expression on airway epithelial cells through the regulation of FOXO-1 activity. Decreased insulin levels or disruption of insulin signaling may be responsible for PAR-2 upregulation in asthmatic airway epithelium, an effect that may subsequently exacerbate proteinase-mediated airway inflammation.

Supervisor: Dr. Harissios Vliagoftis

Identification of an Immunosuppressive Domain in Human Betaretrovirus

Mandana Rahbari1, David Sharon1, Harsh Thaker1, Michael Houghton2 and Andrew Mason1
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by immune destruction of the interlobular bile ducts. While the etiology of PBC is unknown, of environmental factors studied to date only the human betaretrovirus (HBRV) has been reproducibly detected in PBC patients' biliary epithelium. Using overlapping peptides of the HBRV Gag and Env proteins, we have found that 38% of PBC patients had CD8+ T-cell responses with intracellular IFN-γ and TNF-α production to HBRV Gag. Whereas only 7% of patients demonstrated proinflammtory T-cell responses to HBRV Env in identical experiments. These results suggested a hypothesis that the HBRV Env may contain an immunosuppressive domain (ISD) that induces immunoregulatory effect on the immune system.

METHODS

Previous studies have shown that ISD peptides from other retroviruses induce immunoregulatory cytokines production. In order to determine whether HBRV Env contains an ISD, PBMCs from a healthy donor were incubated with 85 overlapping individual peptides corresponding to HBRV SU and TM proteins for 24 hrs prior to collection of the supernatants. IL-10, IL-4, and IL-6 levels were then measured by Mesoscale analysis.

RESULTS

We identified a single peptide homologous to other retroviral ISD sequences located in HBRV TM protein. In order to validate the identification of the HBRV ISD we designed peptides homologous to potential HBRV ISD peptide with a single amino acid difference. The mutations were selected based on the homology of the potential HBRV ISD sequence with known conserved ISD sequences in other retroviruses. Accordingly, we were able to identify the functionally important amino acids in the ISD within the HBRV TM that triggered IL-10, IL-4, and IL-6 production by selectively altering the amino acids in the HBRV ISD sequence.

CONCLUSIONS

These studies are important because they show how HBRV potentially avoids the immune attack to HBRV Env and tolerizes the host to viral infection.

Supervisor: Dr. Andrew Mason

Targeting Pyruvate Dehydrogenase Kinase with Dichloroacetate in Pulmonary Arterial Hypertension: A Variable Clinical Response Driven by Genetic Polymorphisms in Sirtuin 3 and Uncoupling Protein-2

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

INTRODUCTION

Suppressed mitochondrial function inhibits apoptosis, promotes proliferation in the vascular remodeling of pulmonary arterial hypertension (PAH) and is largely due to inhibition of pyruvate dehydrogenase (PDH) by PDH kinase (PDK) induction. Additional causes of PDH inhibition include inhibition of Sirtuin 3 (SIRT3; acetylates/activates PDH) and/or Uncoupling Protein 2 (UCP2; increases mitochondrial calcium). Sirt3 and Ucp2 KO animals develop spontaneous PAH and common loss-of-function polymorphisms in both genes are associated with clinical metabolic syndrome. In a phase-2 trial in 16 PAH patients, Dichloroacetate (DCA; a PDK inhibitor) showed variable efficacy decreasing mean PA pressure (mPAP), not due to DCA-level differences in responders/non-responders. We hypothesized that PDK is upregulated in human PAH but Sirt3/Ucp2 polymorphisms cause resistance to DCA.

METHODS

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

RESULTS

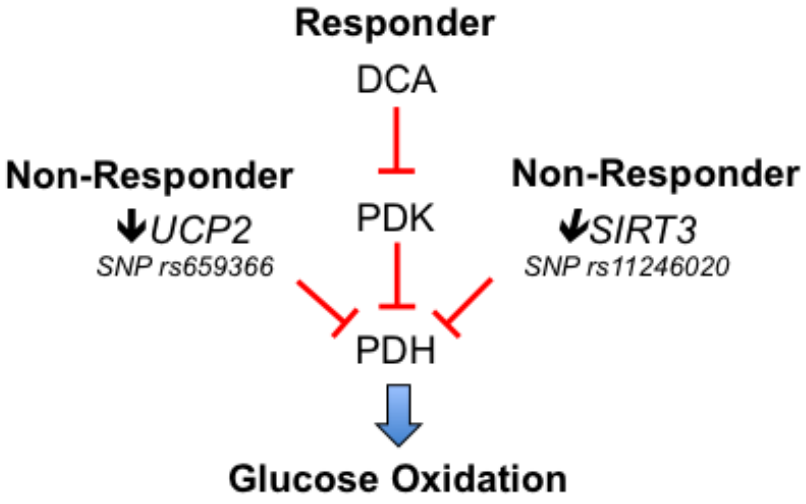
PDK was upregulated (lung and media of pulmonary arteries) and PDH activity was inhibited in PAH lungs compared to controls. In EVLP, DCA increased PDH activity and mitochondrial respiration in lungs with low polymorphism score (0-1), but not in a lung with a high score of 3. In trial patients, lower scores correlated with higher reductions in mPAP (Figure).

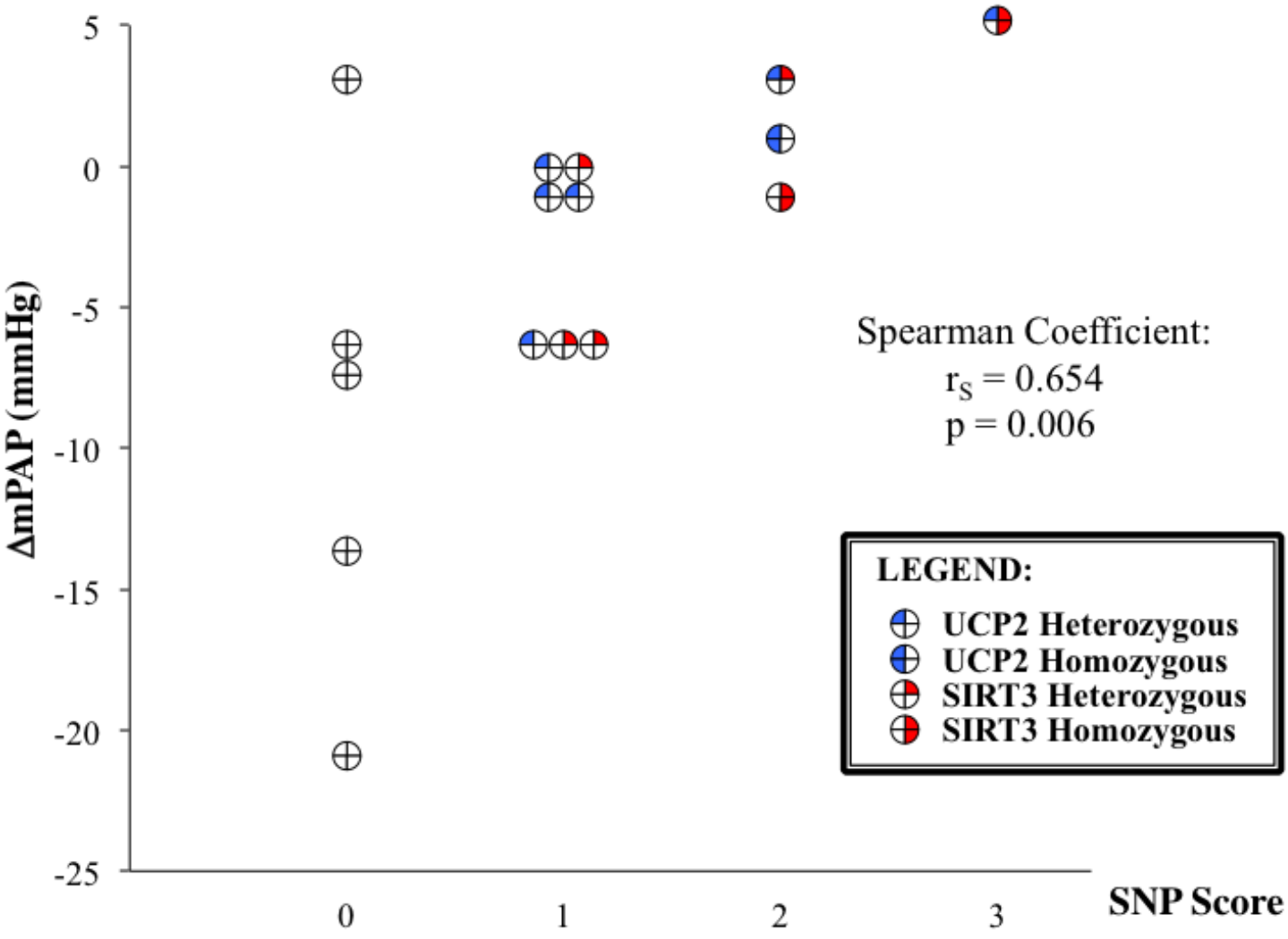
CONCLUSIONS

PDK is induced in human PAH contributing to PDH inhibition but the ex-vivo and clinical response to DCA is limited by polymorphisms that inhibit PDH in a non-PDK dependent manner. This is the first example of precision medicine in PAH, where the clinical response to a drug is driven by the patient genotype.

Supervisor: Dr. Evangelos Michelakis

Figure: Polymorphisms in UCP2 and SIRT3 Can Result in PDK Independent Inhibition of PDH, Limiting the Response to DCA





Antiretroviral drug concentration and efficacy in HIV-infected microglia determine viral persistence in brain tissue

Eugene L Asahchop1, Oussama Meziane8, Manmeet K Mamik1, Wing F Chan1, William G. Branton1, Lothar Resch3, M John Gill4, Elie Haddad5,6, Jean V Guimond9, Glen B Baker2, Eric A Cohen7,8, Christopher Power1,2,4*
Supervisor: Dr Christopher Power

INTRODUCTION
Among patients with HIV-AIDS receiving antiretroviral therapy (ART), viral persistence within the brain remains a vital but unanswered question. We investigated the efficacies and concentrations of contemporary ART drugs in models of HIV-1 infection of the brain.

METHODS
HIV-1 RNA and DNA levels in brain tissues from HIV-infected patients and BLT mice were measured by droplet digital PCR. Host gene transcript levels and neuropathological features were analysed in human and mouse brains. ART drug concentrations and efficacies were quantified in primary human microglia (HFM), bone marrow-derived macrophages (BMDM), peripheral blood mononuclear cells (PBMC) and brain tissues.

RESULTS
In patients receiving stable ART regimens with undetectable plasma viral load, brain tissues collected within 8 hrs of last ART dosing showed detectable HIV-1 RNA and DNA (total and integrated) associated with proinflammatory gene expression. ART drugs showed higher EC50 values in HIV-infected HFM measured by released HIV-1 p24 compared to infected PBMC and BMDM. Intracellular ART drug concentrations in HFM assessed by HPLC-MS were significantly lower than in PBMC. In vivo brain tissue concentrations of ART drugs in mice were >1.0 log lower in multiple brain regions compared with matched plasma levels. In brains from untreated HIV-infected BLT mice, HIV-1 RNA, DNA (total) and p24 expression were detected while ART significantly diminished brain viral burden. Despite similar human cell engraftment in brain across groups, ART interruption resulted in a significant increase in viral RNA and DNA levels in brains of HIV-infected BLT mice.

CONCLUSIONS
ART drugs displayed differential concentrations and antiviral effects depending on the individual drug and HIV-infected cell type (or tissue), which were corroborated by persistent viral DNA and RNA in human and mouse brains. These findings highlight the challenges in selecting effective ART regimens yet underscore the capacity to eradicate HIV-1 from the brain.

Supervisor: Dr Christopher Power

A novel mechanism of myosin phosphatase regulation in endothelial cells: Competition between TIMAP and MYPT1 for the same catalytic PP1 subunit.

Xin Wang MD PhD[2], Laiji Li PhD[1], Barbara J. Ballermann MD[1], Division of Nephrology
Supervisor: Dr. Barbara Ballermann

INTRODUCTION

Non-muscle myosin II regulates many cellular functions including attachment, motility and contraction. In endothelial cells (EC), myosin II activation increases capillary permeability, augmenting capillary leakage during sepsis, and myosin II activity is required for angiogenesis during wound healing, collateral vessel formation and tumor growth. Myosin II activation is brought about by phosphorylation of its myosin-light chain 2 (MLC2) subunit. In turn, MLC2 phosphorylation is controlled by opposing actions of kinases (MLCK and ROCK) and myosin phosphatase(s). The myosin phosphatase holoenzyme that dephosphorylates MLC2 consists of regulatory (MYPT1) and catalytic protein phosphatase-Iβ (PP1cβ) subunits. We identified TIMAP as an EC-predominant member of the MYPT family that also forms a TIMAP/PP1cβ complex in EC. We explored whether TIMAP/PP1cβ functions as a myosin phosphatase in EC, as predicted by its domain homology with MYPT1.

METHODS

Western blots were performed on lysates from lungs (rich in EC) of wild-type and TIMAP-deficient mice, or cultured human glomerular EC. Glomerular EC were transduced with adenoviruses expressing GFP ± wild-type TIMAP ($TIMAP^{WT}$), or ± a TIMAP point mutant that cannot bind PP1cβ ($TIMAP^{PP1-}$). PP1cβ and its associated regulatory subunits were precipitated from EC lysates with anti-PP1cβ, or sepharose-immobilized microcystin, a PP1c-active site inhibitor.

RESULTS

Contrary to expectations, $TIMAP^{WT}$ overexpression in EC significantly enhanced MLC2 phosphorylation, and silencing of endogenous TIMAP in cultured EC, or TIMAP knockout in mice reduced MLC2 phosphorylation. $TIMAP^{WT}$ overexpression markedly slowed the rate of pMLC2 dephosphorylation, indicating that $TIMAP^{WT}$ inhibits myosin phosphatase activity. The MYPT1/PP1cβ complex was effectively precipitated from control EC lysates by PP1cβ antibodies. By contrast, in EC expressing $TIMAP^{WT}$, PP1cβ antibodies co-precipitated only $TIMAP^{WT}$, and not MYPT1, even though MYPT1 was present. As expected, $TIMAP^{PP1c-}$ did not enhance pMLC2 phosphorylation or co-immunoprecipitate with PP1cβ. Microcystin-sepharose precipitated a large amount of PP1cβ along with MYPT1 from control EC lysates, but failed to precipitate either PP1cβ or $TIMAP^{WT}$ from lysates of EC over-expressing $TIMAP^{WT}$.

CONCLUSIONS

The findings that TIMAP binds PP1cβ reducing the MYPT1/PP1cβ association, indicate that $TIMAP^{WT}$ and MYPT1 compete for the PP1cβ catalytic subunit. Since microcystin binds the PP1cβ active site, and readily precipitates MYPT1/PP1cβ, but not TIMAP/PP1cβ, the PP1cβ active site must be open when PP1cβ is associated with MYPT1, but blocked when PP1cβ is bound to $TIMAP^{WT}$. Therefore, by sequestering PP1cβ and blocking its active site, $TIMAP^{WT}$ inhibits myosin phosphatase activity in EC.

Supervisor: Dr. Barbara Ballermann

SEVERE BUT NOT MODERATE ELEVATION OF RENAL VENOUS PRESSURE SUPPRESSES RENAL AND SYSTEMIC SYMPATHETIC OUTFLOW

Shereen M. Hamza1,2, William A. Cupples 3, and Branko Braam1,2
Supervisor: Dr. Branko Braam

INTRODUCTION

Combined heart and renal failure is associated with poor outcome. Heart failure can impair renal function potentially via increased central venous pressure and consequently increased renal venous pressure (RVP). We previously demonstrated that mildly elevated RVP induces an increase in renal vascular resistance (RVR), which is abolished by renal denervation. The hypothesis of the current study was that increases in RVP increase renal sympathetic nerve activity (RSNA).

METHODS

Anesthetized rats were surgically instrumented with catheters to measure mean arterial pressure (MAP), heart rate (HR) and for i.v. infusion. A sling was implanted around the left renal vein, for selective elevation of RVP, measured by adrenal vein catheter. A bipolar electrode was implanted around the left renal nerve bundle for direct recording of RSNA. Following baseline, RVP was unaltered (Controls, n=8) or elevated to either 10 (RVP 10, n=9) or 20mmHg (RVP 20, n=7); all parameters subsequently recorded for 2 hours.

RESULTS

MAP was unaltered in controls and experimental groups. HR was unaltered in controls and RVP 10, however elevation of RVP to 20 mmHg progressively suppressed HR (Baseline: 347±7, 1hr: 330±10, 2hr: 304±13 bpm, $p<0.05$). RSNA response to RVP 10 (1hr: 8±10%, 2hr: 12±12%) did not differ from controls (1hr: 7±5%, 2hr: 5±14%). Conversely, severe RVP elevation immediately and progressively suppressed RSNA (1hr: -39±11%, 2hr: -50±11%). This is characterized by a trend for reduction in action potential amplitude which was not observed in response to mild RVP elevation.

CONCLUSIONS

Pronounced elevation of RVP significantly alters renal sympathetic input by suppressing both frequency and amplitude of action potentials. The parallel RVP-induced reduction in HR is indicative of blunted systemic sympathetic outflow. Results point away from RSNA in RVP-mediated increases in RVR and toward hormonal mechanisms such as Angiotensin II.

Supervisor: Dr. Branko Braam

A novel role of Lung Dendritic Cell recruitment in the lungs of mice with pulmonary arterial hypertension: a potential window into the role of immune cells in vascular remodeling

Mohammed S. Osman, MD PhD FRCPC, Vikram Gurtu MD and Evangelos D. Michelakis, MD
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a deadly disease characterized by a proliferative and inflammatory vascular remodeling in which mitochondria and immune cells play a poorly understood role. Among PAH patients, scleroderma-associated PAH has the worst prognosis. Because tissue dendritic cells are thought to orchestrate immune responses, we studied them in UCP2KO mice, which lack the mitochondrial protein UCP2 (uncoupling protein 2) resulting in recently described mitochondrial suppression and spontaneous PAH. We hypothesized that lung dendritic cells (LDCs), not previously studied in PAH, activate a dysregulated immune-metabolism axis in PAH.

METHODS

We used several LDC markers to study their presence in the lungs from UCP2KO vs wildtype mice using confocal immunofluorescence microscopy and flow cytometry. Mean±SEM values are shown and unpaired t test was used for statistical analysis. We used CD11c and CD103 as LDC markers, and defined perivascular immune cells as localizing within a 10 mm diameter from resistance pulmonary arteries (PA). Ex vivo LDCs were characterized as MHCII+/CD11c+/CD103+ cells using flow cytometry.

RESULTS

7-9 week old UCP2KO mice had increased lung recruitment of LDCs compared to controls: for CD11c: 0.92±0.19 vs 0.29±0.15 cells/PA, $p<0.0001$; for CD103: 0.9±0.064 vs 0.45± 0.064 cells/PA, $p< 0.0001$. Flow cytometry confirmed an increase in CD11c+/MHC+/CD103+ cells in the UCP2KO compared to control lungs: 29±1.2 vs 13.4±1.8 %, $p< 0.0016$. A significant subset of these LDCs (29.3 %) were positive for the survival signal CD40+ which was absent in control lungs.

CONCLUSIONS

We used a model of metabolism-immune axis dysregulation to show for the first time that LDCs are potentially important in PAH. We are currently exploring the downstream signals from LDCs to other cells in vivo and in vitro. The known association of loss-of-function UCP2 polymorphisms (SNPs) with autoimmune diseases suggests that UCP2 may also be an important therapeutic target in scleroderma-associated PAH.

Supervisor: Dr. Evangelos Michelakis

Characterization of N-Myristoyltransferase 2 (NMT2) in Acute Myeloid Leukemia (AML), a Potential Novel Prognostic Biomarker

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Supervisor: Dr. Joseph Brandwein

INTRODUCTION

Myristoylation is the post-translational modification of proteins with a 14-carbon fatty-acid by N-myristoyltransferase (NMT) 1 or 2. Myristoylation is key to protein membrane binding and cell survival.1 Bioinformatics data suggests NMT mRNA expression impacts overall survival (OS) in AML.2 We characterized NMT protein levels in AML patients.

METHODS

We performed a retrospective and prospective cohort study, including adult patients newly diagnosed with AML in Edmonton from April 2014 until September 2016, excluding t(15;17). We assayed marrow aspirate for NMT1/2 protein levels by multicolour flow cytometry with intracytoplasmic staining by custom mouse anti-NMT1-Alexa-Fluor-647 or anti-NMT2-FITC antibody with IgG1k-FITC isotype control (BD Biosciences), expressed as Mean Fluorescent Intensity (MFI).

Clinical data was analysed by t-test or ANOVA. Relapse-free survival (RFS) and OS were dichotomized with a receiver operator curve (ROC), followed by a Kaplan-Meier estimator, $p<0.05$ significant by log-rank. Censoring, survival, and clinical parameters were defined by European LeukemiaNet (ELN) guidelines and REMARK criteria.3,4

RESULTS

Recruitment reached 105 patients. Median age was 67.1 years, with 57 ELN intermediate-risk patients. Median follow-up and OS are 1.33 and 1.19 years, respectively.

NMT1-MFI was consistent through all samples. NMT2-MFI was higher in lymphocytes vs. monocytes and blast populations (median=3.01,0.98,1.13;$p<0.001$). NMT2-MFI was strongly associated with the cytogenetic abnormality inv(16) (median=1.67,$p<0.001$). NMT2-MFI was not associated with ELN risk groups or remission status. ($p=0.481,0.358$).

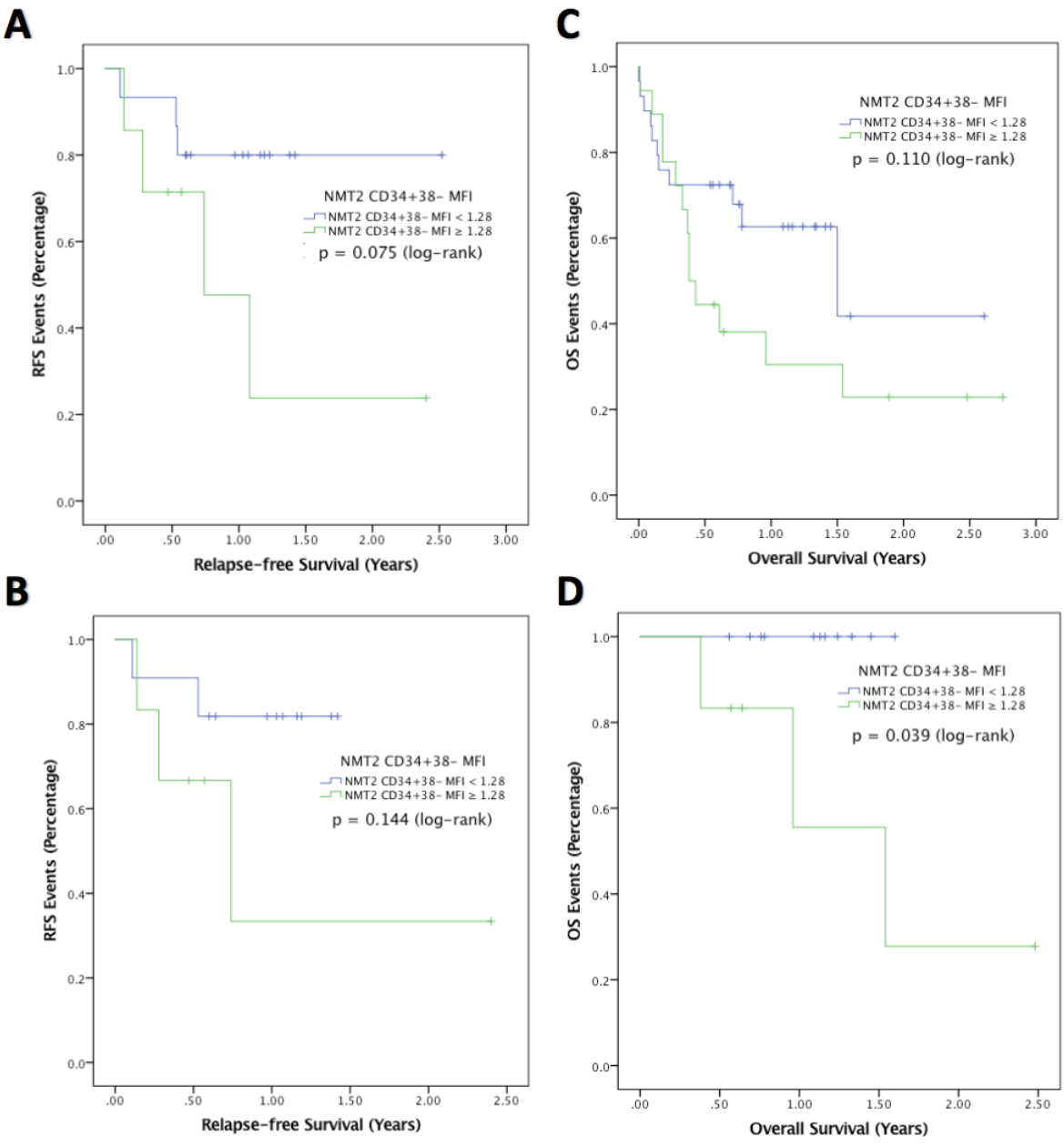
NMT2-MFI ROC analysis for OS in ELN intermediate-risk AML in CD34+38- cells generated a cut-off 1.28 (AUC=0.766,$p=0.002$) for sensitivity=54% and specificity=88%. Kaplan-Meier analysis for RFS and OS showed a trend towards significance, which reaches significance for OS when restricting to patients age<65. (fig.1)

CONCLUSIONS

NMT2 protein expression is higher in AML with inv(16) but is not associated with ELN risk categories or remission status. Lower NMT2 expression shows a trend towards improved RFS and OS in intermediate-risk AML, and is statistically significant for OS in younger patients.

Supervisor: Dr. Joseph Brandwein

Figure 1. Kaplan-Meier Survival Analysis for NMT2 MFI in the CD34+38- blast population amongst ELN intermediate risk patients. A. Relapse-free survival for all intermediate risk patients, B. Relapse-free survival for all intermediate risk patients with age < 65, C. Overall-survival for all intermediate risk patients, D. Overall-survival for all intermediate risk patients with age < 65.



Treatment Outcome in Chronic Hepatitis C Genotype 1 (GT1) Patients Treated with 8 Weeks vs. 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) based on Viral Load (VL) Criteria as Determined using The Abbott RealTime Assay

Maryam Rezaeeaval, Suzanne Sumner, Stephen Shafran, Karen Doucette
Supervisor: Dr.Karen Doucette

INTRODUCTION

Based on post-hoc analysis of ION-3 study and observational data, shortened therapy of 8 rather than 12 weeks of Ledipasvir/Sofosbuvir may be considered for treatment-naive, non-cirrhotic, GT1 chronic HCV patients with baseline HCV RNA < 6 million IU/mL. This HCV RNA threshold was established in a trial using Cobas®TaqMan assay. Recent data highlight interassay variability between this and Abbott RealTime (ART) assay, used in many clinical laboratories. Based on this, some have suggested a threshold of 2.2 million IU/mL using ART assay. Our objective was to determine sustained virologic response at 12 weeks (SVR12) with 8 vs 12 weeks LDV/SOF in those with baseline HCV RNA <6 million IU/mL using ART assay.

METHODS

A retrospective, single centre cohort study was done including all HCV treatment naïve, GT1 noncirrhotic patients treated with LDV/SOF.

RESULTS

Among 212 patients, 69.7% were male, median age was 57 years , median BMI 27. Genotype: 1a in 71.2%, 1b in 17.9%, other 1in 10.8%. Fibrosis stage: 26.4% F0/1, 48.1% F2, 25.5% F3. Median baseline HCV RNA: 826,479 IU/mL with 199 patients (93.9%) < 6 million IU/mL. Of these, 129 (64.8%) received 8 weeks of therapy. SVR12 was similar in those treated with 8 vs 12 weeks [94.5% vs 94.3%; p=0.95]. If threshold of 2.2 million IU/mL were used to shorten therapy, only 75% of patients would have been eligible. Private vs public medication insurance was associated with 12 weeks of therapy, despite meeting VL criteria for 8 weeks (p=0.03).

CONCLUSIONS

In our cohort, 94% of HCV treatment naïve, GT1 noncirrhotic patients were eligible for 8 weeks of LDV/SOF using a threshold of <6 million IU/mL. The SVR12 in those meeting VL criteria and treated for 8 vs 12 weeks was similar, suggesting this is safe and more cost effective than a proposed ART assay threshold of 2.2 million IU/mL.

Supervisor: Dr.Karen Doucette

Intravenous fluid use for the resuscitation of diabetic ketoacidosis: a multi-centre, retrospective, observational cohort study.

Brandon P Galm, Peter A Senior, Sean M Bagshaw
Supervisor: Dr. Sean M Bagshaw

INTRODUCTION
Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM). There is a paucity of evidence to guide the intravenous fluid (IVF) type used for resuscitation of DKA, with most guidelines recommending 0.9% saline. We aimed to describe the distribution of crystalloid fluids used for resuscitation and the associated course among patients presenting with DKA.

METHODS
Retrospective cohort study of adult patients (≥18 years) admitted with moderate to severe DKA to general medicine or the intensive care unit (ICU) from May 2013 to June 2014 at three hospitals in Edmonton, Canada. Primary exposure was type and amount of IVF received. Primary endpoint of interest was biochemical resolution of DKA.

RESULTS
We included 103 hospitalizations, with mean (SD) age 38.7 (15.1) years, 56% male, and hemoglobin A1c 11.1 (2.2) percent. DM etiology was type 1 in 71 (69%), type 2 in 25 (24%), secondary in 2 (2%), and unclear in 5 (5%). DKA was moderate in 41 (40%) and severe in 62 (60%). Nineteen patients (18%) were transferred from community hospitals, and 10 patients (9.7%) were admitted to the ICU. Of the 14 hospitals included, only 1 community hospital had a protocol to guide DKA management. Median (IQR) time from emergency department triage to IVF administration was 77 (34–135) minutes. At 12 hours, median IVF volume received was 5.0 (3.8–5.9) litres, of which 5.6% was RL and 1.5% was PL. Median time to resolution of DKA was 8.7 (6.0–12.3) hours using an anion gap ≤12, with no difference between those who received a significant amount (>1/3 of IVF at 12 hours) of RL or PL compared to those who did not (p=0.68).

CONCLUSIONS
The majority of IVF used for initial resuscitation of DKA remains 0.9% saline. There was no difference in time to resolution of DKA using RL or PL; however, these fluids were used infrequently.

Supervisor: Dr. Sean M Bagshaw

Reducing Unnecessary, Prophylactic Transfusions of Frozen Plasma in Patients undergoing Imaging-guided Procedures

Mohammad Refaei, M.D.1 Jennifer Crawford, BSc.(MLS), MLT 2 Heather Blain, BSc.(MLS), MLT 2 Susan Nahirniak, M.D. FRCPC 3 Melanie Bodnar. M.D. FRCPC 3
Supervisor: Dr. Melanie Bodnar

INTRODUCTION

Inappropriate use of prophylactic plasma prior to bedside and image-guided procedures has been noted in several audits (including our own 2014 audit) despite medical evidence that it is ineffective and potentially harmful.

METHODS

We shared the findings of 2014 audit with stakeholder departments, developed consensus institutional guidelines for plasma and a multipronged educational campaign involving key stakeholders in adult medical, surgical and diagnostic imaging services. This was then followed by implementation of a mandatory plasma request form.

Pre- and post-intervention audits reviewed all plasma requests between April 1 and June 30th in 2014 and 2016 respectively. Requests prior to defined interventional procedures (including paracentesis, thoracentesis, line insertion, lumbar puncture, liver biopsy) were identified and adjudicated as appropriate versus inappropriate based on our new institutional pre-procedure guidelines and plasma thresholds categorized as low (INR>3) versus high risk (INR>1.8).

RESULTS

During our audit periods, a decrease in plasma use was identified and is currently sustained. There were a total of 425 and 388 plasma forms in 2014 and 2016 respectively. Pre-procedure requests accounted for 73 (17.4%) and 69 (17.9%), respectively. In both, paracentesis accounted for ~60% of requests and > 75% of patients had coagulopathy due to cirrhosis. 27.4% of 2014 pre-procedure plasma requests had an INR <1.8 versus 5.8% in 2016 (p=0.4). In the pre-intervention audit 85.9% (n=70) of plasma requests were inappropriate versus 46.4% (n=32) in the post-audit (p =0.0004). In 2016, 52.4% of these inappropriate requests were for patients undergoing paracentesis.

CONCLUSIONS

Our overall plasma usage and number of inappropriate plasma requests pre-bedside procedure have both significantly decreased. However, paracentesis continues to be an area for improvement and further reductions in plasma utilization can be realized by abolishing the INR cut-off for low risk procedures. Further educational interventions and force functions will be required.

Supervisor: Dr. Melanie Bodnar

Suicide prevention strategies for Canadian First Nations Youth: Results of Environmental Scan

Maulik Baxi
Supervisor: Dr. Kathryn Koliaska

INTRODUCTION

Suicide is a leading cause of mortality in youth the world over with significant social and economical burden on families and communities. The rates of suicide deaths have remained steady over last several years despite several prevention and intervention programs, especially among the First Nations communities.

METHODS

The purpose of this environmental scan and literature review is to understand the determinants and effectiveness of preventive interventions from public health perspective. Several social determinants of health act as predisposing risk factors behind these trends. We reviewed published data on suicide rates and prevention strategies in Canada. We also examined prevention approaches in other developed countries, most notably including Australia, New Zealand, United Kingdom and United States of America in the last twenty years.

RESULTS

Among the evidence supported strategies and interventions, guided support, education and awareness appear most commonly the first approach adopted by most jurisdictions and service provides. Several other evidence-informed approaches are also available to public health and mental health service provides. These include screening for suicidal ideations, addictions support services, various means restriction interventions, pharmaceutical and drug control, mechanical barriers, weapons control, media and communications relations and social media control.

CONCLUSIONS

Due to the scale and persistence of the problem among the First Nations youth, strategies that include collaborative actions by governments, educational institutions, health service providers, law enforcement and community would be likely be the most helpful preventing suicides.

Supervisor: Dr. Kathryn Koliaska

Venous thromboembolism prophylaxis in hospitalized patients with cancer: A post-intervention quality improvement study

Maryam Soleimani, Anna Whalen-Browne, Levi Johnston, Gina Polley, Cynthia Wu
Supervisor: Dr. Cynthia Wu

INTRODUCTION

Hospitalization and active malignancy are known to be strongly associated with the development of venous thromboembolism (VTE). VTE prophylaxis has now become a routine practice at most acute care centres, and is an accreditation standard. In 2014, Polley et al. conducted a retrospective chart review assessing rates of VTE prophylaxis amongst patients admitted to the Cross Cancer Institute (CCI) from January to June 2010. In January 2015, Alberta Health Services (AHS) introduced a standardized order set to improve rates of VTE prophylaxis prescription amongst inpatients. In this post-intervention quality improvement project, we aimed to assess the utilization of this order set.

METHODS

Retrospective chart review of patients admitted to the CCI between January to June 2015. Charts were reviewed for use of the order set, and clinical decisions made around VTE prophylaxis. Demographic information, status of malignancy, contraindications to prophylaxis, and bleeding and thrombotic complications were also collected.

RESULTS

505 patients met criteria for inclusion. Mean age was 61.3 years. Mean length of stay was 10.9 days. Six percent of patients had a prior history of VTE. Preliminary results show that the standardized order set was used in only 38% of cases, and 40.8% of patients received VTE prophylaxis (compared to 24.3% pre-intervention). Only 12.1% of patients had a true contraindication to prophylaxis. Low molecular weight heparin was the most commonly prescribed type of prophylaxis. Four patients (0.8%) experienced a VTE during their admission.

CONCLUSIONS

Our results show an overall increase in rate of VTE prophylaxis prescribing after the standardized order set was introduced, with only a minority of patients having true contraindication to prophylaxis. These results show improvement in rates of prophylaxis prescription after the introduction of the order set. Though this is encouraging, there is room for improvement. Further discussion with stakeholders to examine more optimal strategies for VTE prophylaxis prescribing will need to be undertaken.

Supervisor: Dr. Cynthia Wu

'TUCK in rounds': A non-pharmacologic intervention to improve sleep of medicine inpatients

S. Dobing, A. Dey-Broughton, F. McAlister, J. Ringrose
Supervisor: Dr. Jennifer Ringrose

INTRODUCTION

Sleep quality in hospitalized medicine patients is poor, with environmental factors among the most frequently cited reasons. We tested the efficacy of a non-pharmacologic intervention on the sleep quality of medicine inpatients.

METHODS

This was a controlled study to evaluate our non-pharmacologic multidisciplinary “TUCK-in” protocol (which includes timed lights-off periods, minimizing nighttime noise, distribution of earplugs at bedtime, cued toileting before bedtime, and identification and reduction of modifiable interruptions), deployed on 2 of 5 identical medicine wards. Randomization was at the level of the ward. The main outcome measure was self-reported duration of nighttime sleep within 48 hours prior to discharge. Additional outcome measures included the Verran Snyder-Halpern (VSH) Sleep Score and inpatient sleep pharmaceutical use.

RESULTS

Self-reported duration of nighttime sleep (median 5.0 vs. 5.0 hours, p=0.29) and daytime sleep (1.0 versus 0.5 hours, p=0.43) did not differ between the 40 intervention patients and the 41 control patients (p=0.13 on multivariate analysis) Cumulative VSH sleep disturbance (median 420 versus 359, p=0.19), efficacy (median 169 versus 192, p=0.29), or supplementation (median 97 versus 100, p=0.51) scales were also not different between study arms.

CONCLUSIONS

Although staff reported the protocol to be achievable and worthwhile, there were no significant differences in any of the outcomes between intervention and control patients.

Supervisor: Dr. Jennifer Ringrose

THE USE OF FRUCTOSAMINE IN CYSTIC FIBROSIS-RELATED DIABETES (CFRD) SCREENING

Grace Y Lam; Michelle Doll-Shankaruk; Jan Dayton; Karina Rodriguez-Capote; Trefor N Higgins; Dylan Thomas; Maeve P Smith; Neil E Brown; Winnie M Leung; Mathew Estey, Ph.D.
Supervisor: Dr. Mathew Estey

INTRODUCTION

Cystic fibrosis related diabetes (CFRD) is a disease of transient hyperglycemia, which if unrecognized and untreated results in irreversible decline in lung function and increased morbidity and mortality. Currently, CFRD is diagnosed with the oral glucose tolerance test (OGTT), as traditional markers of glycemic control, such as HbA1C and fasting glucose are unreliable in patients with CF. Given that compliance with the OGTT is poor, and screening thresholds are not based on relevant CF outcomes, such as impaired lung function, there is great interest in identifying an alternate screening test for CFRD. Serum fructosamine is a simple blood test that measures total glycated serum protein, and is used in clinical settings where HbA1C is unreliable. Here, we aim to determine whether serum fructosamine correlates with glycemic control and clinical outcomes in patients being screened for CFRD.

METHODS

Fructosamine and percent predicted forced expiratory volume in one second (FEV1) were measured in patients undergoing a 2 hour oral glucose tolerance test (OGTT) for CFRD screening. Fractional serum fructosamine (FSF) was calculated as fructosamine/total protein.

RESULTS

FSF exhibited a positive correlation with 2 hour OGTT results ($r^2=0.3201$, $p=0.009$), and ROC curve analysis suggested that FSF can identify patients with an abnormal OGTT (AUC=0.840, $p=0.0002$). FSF also exhibited a negative correlation with FEV1 ($r^2=0.3732$, $p=0.035$). Patients with FSF ≥3.70 µmol/g has significantly lower FEV1 (median 47%) compared to those with FSF <3.70 µmol/g (median 90%; $p=0.015$).

CONCLUSIONS

FSF correlated with both OGTT results and FEV1, and reliably identified patients with abnormal OGTT results. This simple blood test may improve screening compliance, and shows potential as an effective tool in CFRD screening.

Supervisor: Dr. Mathew Estey

Lipopolysaccharide Inhibits Interleukin–13-induced CCL26 in Human Airway Epithelial cells

Dhaifallah Alotaibi and Harissios Vliagoftis
Supervisor: Harissios Vliagoftis

INTRODUCTION

Interleukin-13 (IL-13) is a central effector cytokine in asthma and promotes eosinophilic inflammation, airway hyper-responsiveness, mucus secretion, epithelial damage and fibrotic changes in the airways. An important target of IL-13 in the lungs is the airway epithelium. IL-13 stimulates bronchial epithelial cells to release eotaxin-3 (CCL26) through Janus kinase-2/signal transducer and activator of transcription-6 (Jak2/Stat6) -mediated signaling. CCL26 is a potent chemoattractant for eosinophils, a hallmark of asthma. The effects of bacterial infections on airway eosinophilia are incompletely understood. There is evidence that microbial products through TLR activation affect the release of eosinophil chemotactic factors. Here we studied the effects of TLR4 activation on IL-13-induced CCL26 in airway epithelial cells

METHODS

The human bronchial epithelial cell line BEAS-2B was stimulated with different concentrations of the TLR4 ligand, LPS (up to 10 ug/ml) alone or in combination with IL-13 (20 ng/ml) for up to 24 hrs. CCL26 mRNA was measured using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). ELISA was used to quantitate CCL26 release in cell supernatants. STAT6 and JAK2 phosphorylation was measured by western blot. Translation inhibitor (cycloheximide) and NF-kB inhibitors (curcumin, arctigenin, bengamide B) were used to understand the signaling pathways mediating the interaction between IL-13 and LPS

RESULTS

BEAS-2B cell activation with IL-13 strongly induced CCL26 mRNA expression. LPS inhibited IL-13-induced CCL26 expression in time and concentration-dependent manner. IL-13 induced STAT6 phosphorylation in BEAS-2B cells, which peaked at 30 min. This phosphorylation was attenuated when cells were activated by IL-13 in the presence of LPS. LPS also inhibited IL-13-induced JAK-2 phosphorylation. The LPS inhibitory effect on IL-13-induced CCL26 up regulation and secretion was dependent on NF-kB activation and new protein synthesis

CONCLUSIONS

LPS, a TLR4 ligand, inhibits the effects of IL-13 on CCL26 expression in airways epithelial cells. This effect is mediated through NF-kB activation and requires protein synthesis

Supervisor: Dr. Harissios Vliagoftis

Cockroach Extract Down-regulates Interleukin-13 Dependent Eotaxin-3 mRNA and Protein Expression in BEAS-2B Cell Line

Khadija Alzahrani, Vivek Gandhi, Cheryl Laratta, and Harissios Vliagoftis
Supervisor: Dr.Harissios Vliagoftis

INTRODUCTION

Cockroach allergens are associated with asthma in many studies. Cockroach allergens can activate cells through Protease-Activated Receptor-2 (PAR-2) and others. Interleukin-13 (IL-13), a central mediator of asthma augments mucus production, bronchial hyper-responsiveness, and proliferation of airways smooth muscle cells. IL-13 is also known to induce a potent eosinophil chemoattractant, Eotaxin-3 (CCL26). We hypothesized that cockroach extract (CE) enhances IL-13 dependent induction of CCL26 from airway epithelium.

METHODS

Bronchial epithelial cells (BEAS-2B) were cultured in pre-coated multi-well plates until 80-90% confluent. They were then activated by IL-13, CE or both. CCL26 mRNA was measured by qRT-PCR and CCL26 protein by ELISA. To test the role of CE proteinases, heat inactivated CE or CE pre-incubated with proteinase inhibitors were used. Flow cytometry used to detect IL-13α1 receptor, and western blotting to assess STAT-6 phosphorylation and IL-13 protein degradation.

RESULTS

IL-13 induced upregulation of CCL26 mRNA and protein release from BEAS-2B after 24 h. CE alone had no effect on CCL26 mRNA and protein expression, but prevented IL-13-mediated up-regulation of CCL26 mRNA and protein. Heat inactivated CE and CE pre-incubated with Aprotinin, a serine proteinase inhibitor, were unable to prevent IL-13 induced CCL26 upregulation. IL-13 also induced STAT-6 phosphorylation in BEAS-2B cells. Phosphorylation did not change significantly when cells were incubated with IL-13 plus CE. PAR-2 activating peptides had no effect IL-13 induced CCL26 upregulation indicating that the CE effect is probably independent of PAR-2 activation. In addition, CE proteinases had no effect on IL-13α1 receptor expression on the surface of BEAS-2B cells.

CONCLUSIONS

CE inhibits the effect of IL-13 on CCL26 upregulation in a PAR-2 independent fashion. This effect is probably mediated by a proteinase activity present in CE and it does not depend on cleavage of IL-13 receptor. This may be a mechanism for CE to decrease the detrimental effects of Th2 cytokines in the airways.

Supervisor: Dr.Harissios Vliagoftis

FGD5 regulates VEGF receptor-2 coupling to PI3 kinase and recycling

Abul K Azad*1, Maikel Farhan*1, Nicolas Touret2 and Allan G Murray1
Supervisor: Allan Murray

INTRODUCTION

Angiogenesis is required for embryonic development and tumor growth in the adult. Vascular endothelial growth factor (VEGF)-A signaling to the endothelial cell (EC) through VEGF-receptor-2 (VEGFR2) is the principal cue driving new blood vessel formation. Facio-genital dysplasia-5 (FGD5), a Rho-family guanine nucleotide exchange factor, is selectively expressed in EC. Deficiency of FGD5 is embryonically lethal in mice, and perturbs angiogenesis and VEGF signal transduction. However, the mechanism of FGD5 regulation of VEGF signaling is poorly understood. We seek to investigate the role of FGD5 in VEGF signaling in EC.

METHODS

Angiogenic sprouting and EC cytoskeletal remodeling were evaluated in a 3D in vitro model. Cells were coated on Cytodex beads, mounted in fibrin gels, and stimulated with VEGF for 18 hours. The number of angiogenic sprouts/bead, sprout lengths, and tip cell specific marker genes were measured. We examined the subcellular localization of FGD5 in EC by immunofluorescence microscopy, and studied VEGFR2 signal transduction by Western blot.

RESULTS

FGD5 deficiency reduced the number of angiogenic sprouts and tip cell filopodia by~80% and ~70%, respectively. These defects were accompanied by reduced expression of angiogenic tip cell-specific differentiation markers. In resting and VEGF-stimulated EC, FGD5 formed a complex with VEGFR2 and was enriched among early endosomes. FGD5 loss did not alter VEGFR2 plasma membrane expression, Y1175 phosphorylation, or endocytosis. However, FGD5 loss decreased VEGFR2 coupling to phosphoinositide-3 kinase (PI3K) in early endosomes, reduced mammalian target of rapamycin complex2 (mTORC2)-dependent Akt and cortactin activation downstream of VEGFR2 activation. Further, FGD5 loss diverted VEGFR2 to Rab7+ endosomes, and subsequent lysosomal degradation. Rab7 knockdown partially rescued VEGFR2 signal transduction to Akt.

CONCLUSIONS

FGD5 regulates endothelial tip cell-cytoskeletal remodeling and differentiation in VEGF-guided angiogenesis. Mechanistically, FGD5 regulates VEGFR2 retention in recycling endosomes, and coupling to PI3K/mTORC2-dependent Akt and cortactin activation.

Supervisor: Dr. Allan Murray

Natural health product use with antineoplastic topoisomerase inhibitors: a systematic review of natural health product-drug interactions

Basiuk M, Singh R, Sun X, Vohra S
Supervisor: Dr. Sunita Vohra

INTRODUCTION

Cancer patients are at high risk of adverse events (AE) associated with natural health products (NHPs), including NHP-drug interactions, due to their high use among this population. Moreover, anticancer medications have complex pharmacokinetics and often a narrow therapeutic index making cancer patients potentially vulnerable to clinically important NHP interactions and AE. As we become more aware of the common use of NHPs in this population, it is important that we determine what information already exists about NHP-anticancer medication interactions.

METHODS

We searched MEDLINE, EMBASE, CINAHL, CENTRAL, conducted hand searches and searched for unpublished data. Independently two authors screened titles/abstracts and subsequently full-text reports for inclusion: English, primary data, pediatric and adult cancer patients receiving topoisomerase inhibitor-based cancer treatment and concurrent single NHP (garlic, ginseng, milk thistle, mistletoe, probiotics, turmeric, vitamin C, vitamin D or vitamin E).

RESULTS

712 records were obtained and 126 articles met our inclusion criteria. 16 human studies were included in the final qualitative synthesis. Several potential interactions were discovered: change in vitamin serum level (3); beneficial (4); pharmacokinetic (1); mild to moderate AE (5); serious AE (1). Four studies documented NHPs were unable to reduce side effects of anticancer medications and 4 showed a lack of AE after concurrent NHP-drug use. Generally, the included studies introduced major biases and based on their size and duration, it is likely that rare AE would not have been detected.

CONCLUSIONS

Although this review highlights the overall paucity of available clinical information on NHP-topoisomerase inhibitor interactions, it has depicted the potential for interaction exists. Knowing that NHPs may impact cancer treatment, either positively or negatively, it refutes the assumption that NHPs are innocuous. Enhanced pharmacovigilance is required to identify safety signals that can be further examined by extensive, large-scale observational studies.

Supervisor: Dr. Sunita Vohra

Assessing Physician Knowledge Regarding Indications for a Primary Prevention Implantable Defibrillator and Potential Barriers for Referral

Rochelle CM Bernier, Satish Raj, Lucy Reyes, Michel Sauve, Glen L Sumner, Derek V Exner, Roopinder K Sandhu
Supervisor: Dr. Roopinder K Sandhu

INTRODUCTION

There is clear evidence to demonstrate that prophylactic implantable cardioverter defibrillators (ICDs) reduce mortality in high-risk patients however, it is under-utilized. Limited data exists assessing referring physicians knowledge regarding guideline indications and attitudes towards ICD therapy, which may influence decision for referral.

METHODS

The Cardiovascular Arrhythmia and Stroke Working Group from Alberta developed a web-based survey consisting of case scenarios regarding primary prevention ICD indications and a list of barriers for referral as part of a quality assurance initiative to aid in the design of a complex device care pathway. We invited referring physicians to participate in the survey including Internists and Cardiologists with Alberta Medical Association membership and Cardiology residents.

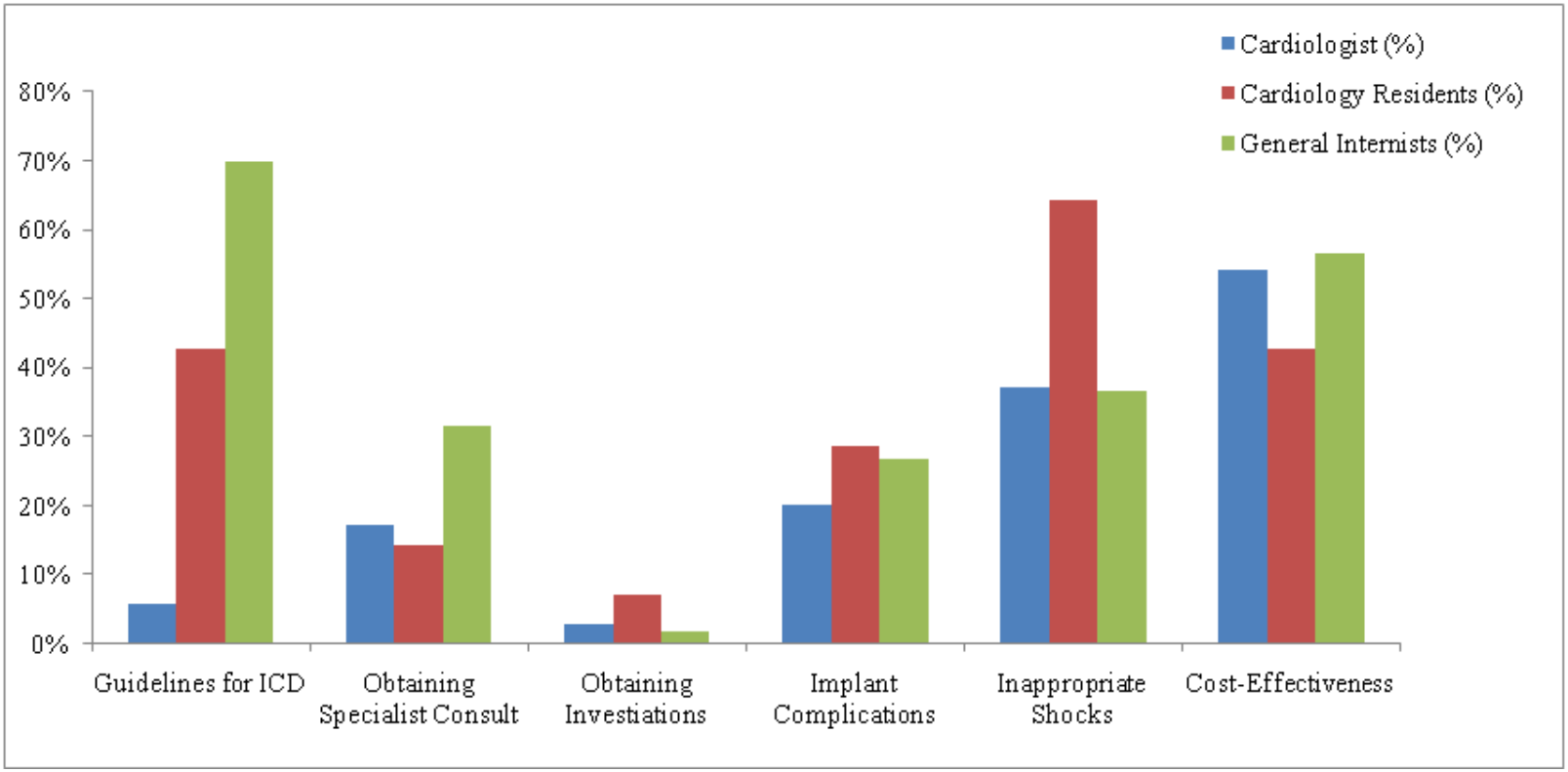
RESULTS

The survey was completed by 109 of 799 (response rate =14%) of physicians. Of those, 55% were Internists, 32% Cardiologists and 13% Cardiology residents. The majority of physicians were male (62%), practicing in a University Hospital (66%). Overall, complete guideline-concordant answers were provided by 34% of physicians. In multivariable analysis, predictors of complete guideline concordance were being a Cardiologist (odd ratio (OR) 5.9, confidence interval (CI) 2.1-16.4, p=0.001) or Cardiology resident (OR 6.7, CI 1.7-27.3, p=0.007). The most common barrier for referral for Internists was a lack of confidence in knowledge of guideline recommendations; Cardiologists reported concerns about cost-effectiveness and residents were most concerned with inappropriate shocks (Figure 1).

CONCLUSIONS

Knowledge regarding indications for prophylactic ICD is limited and varies significantly among referring physicians. In addition, the barriers for referral appear to differ among physician groups. Addressing these barriers is important in optimizing ICD utilization.

Supervisor: Dr. Roopinder K Sandhu


Cardiologist (%)
Cardiology Residents (%)
General Internists (%)
80%
70%
60%
50%
40%
30%
20%
10%
0%
Guidelines for ICD
Obtaining Specialist Consult
Obtaining Investiations
Implant Complications
Inappropriate Shocks
Cost-Effectiveness

A Population-based Study of Adherence to Appropriate Use Criteria and Guideline Recommendations for Implantable Cardioverter Defibrillators

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

INTRODUCTION

Few studies have evaluated physician adherence to appropriate use criteria and guideline recommendations for implantable cardioverter defibrillators (ICDs) in a real world setting. Our objective was to determine the proportion of patients receiving ICD therapy according to appropriate use criteria and guideline recommendations.

METHODS

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

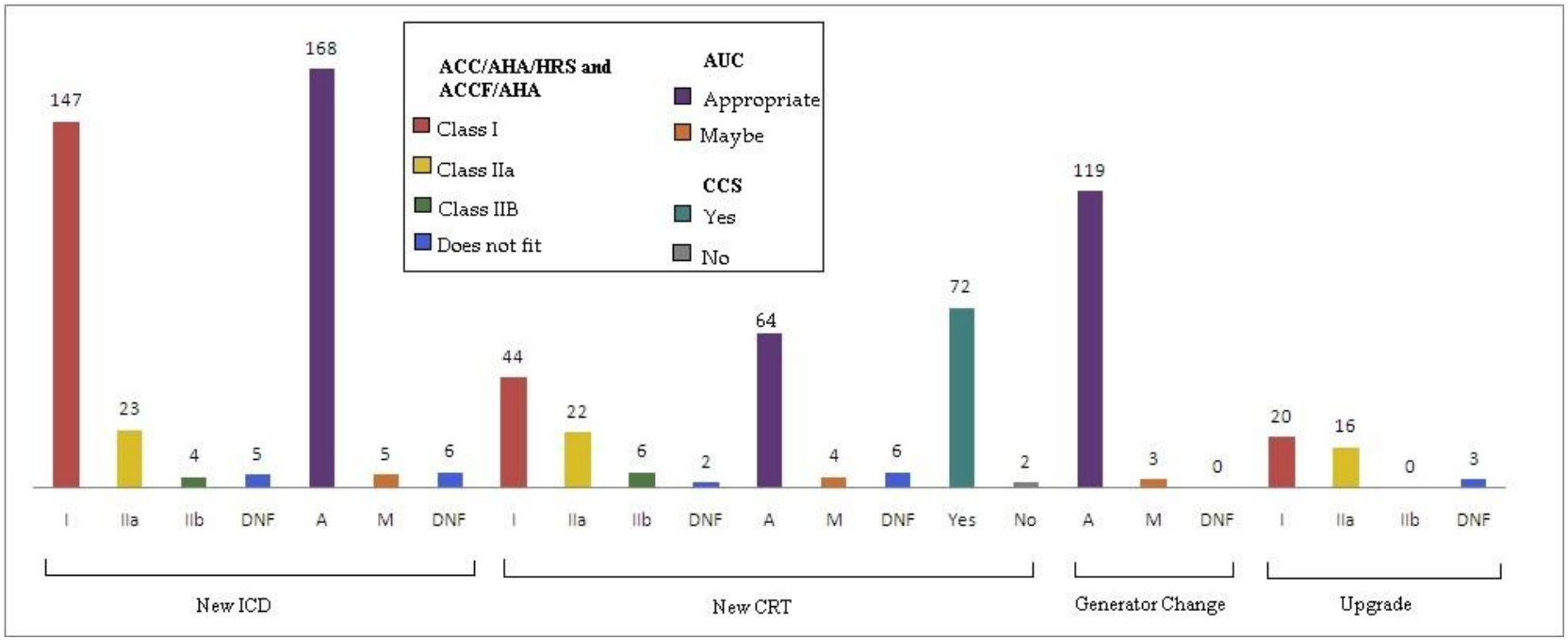
RESULTS

A total of 398 devices were implanted. The mean age of patients was 63 ±12; 83% were male; with a mean Charlson Comorbidity Index of 3.3 ±1.95; mean ejection fraction of 0.32 ±0.13 and 62% of implants were for primary prevention. Of the procedures performed, 64% were new implants, 31% were generator changes, and 5% were upgrades. The majority of ICDs met ‘appropriate’ and class I indications for implant while no procedures occurred for ‘rarely’ or class III indications (Figure 1). No appropriate use criteria existed for 3% of implants.

CONCLUSIONS

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

Supervisor: Dr. Roopinder K Sandhu


ACC/AHA/HRS and ACCF/AHA
Class I
Class IIa
Class IIB
Does not fit
AUC
Appropriate
Maybe
CCS
Yes
No
147
23
4
5
168
5
6
44
22
6
2
64
4
6
72
2
119
3
0
20
16
0
3
I
IIa
IIb
DNF
A
M
DNF
I
IIa
IIb
DNF
A
M
DNF
Yes
No
A
M
DNF
I
IIa
IIb
DNF
New ICD
New CRT
Generator Change
Upgrade

BEYOND THE ANTIBODIES: SERA METABOLOMIC BIOMARKER SIGNATURES DISCRIMINATE MYASTHENIC AND HEALTHY COHORTS

Derrick Blackmore BSc, Nan Wang PhD, Liang Li PhD, Zaeem A. Siddiqi MD PhD
Supervisor: Dr. Zaeem Siddiqi

INTRODUCTION

Few biomarker studies have assessed the serum metabolome in patients with myasthenia gravis (MG). Recent advancements in metabolomic profiling with high coverage may facilitate description of an enhanced MG biomarker signature. OBJECTIVE: To construct and compare the serum metabolomic profiles of MG patients and healthy individuals using a novel chemical isotope labeling liquid chromatography-mass spectrometry (CIL LC-MS) technique.

METHODS

CIL LC-MS uses different labeling reagents to target chemical group-based submetabolomes to provide in-depth metabolomic analysis. 12C-dansylation labeling of individual samples and 13C-dansylation labeling of pooled samples from 49 patients with seropositive MG and 50 age/gender matched healthy control subjects was undertaken. The amine/phenol submetabolome changes among the labeled samples were quantified based on subsequent analysis of the 13C- and 12C-labeled mixture by LC-MS.

RESULTS

On average, 4084±149 (n=49) and 3972±492 (n=50) metabolites were detected in sera from MG samples and control subjects, respectively—a total of 5711 metabolites in all samples. Orthogonal partial least squares discriminant analysis showed a clear separation of 2 groups (R2=0.98, Q2=0.80). The receiver operating characteristic (ROC) curve using 7 metabolites produced an area under the curve (AUC) value of 0.859 (0.806-0.920, 95% CI) with 91% specificity and 70% sensitivity.

CONCLUSIONS

High-coverage metabolomic profiling reveals that serum metabolomes of MG patients differ considerably from healthy control subjects, substantiating the probability of finding metabolic biomarkers specific to MG.

Supervisor: Dr. Zaeem Siddiqi

Discovery of a novel c-Myc-ND2 fusion protein (a product of fusion between a mitochondrial and a nuclear gene) that regulates cell growth in response to metabolic stress

Boukouris AE, Stenson T, Saleme B, Kinnaird A, Zervopoulos S, Gurtu V, Sutendra G, Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Coordination between metabolism and growth is critical for cell survival. Bi-directional signals between the nucleus (n) and mitochondria (mt) (which maintain their own mtDNA, encoding for a few mitochondrial proteins, whereas most are encoded by nDNA) have evolved to an incompletely understood mitochondria-nucleus axis. How this responds to major metabolic stress to facilitate cell survival/growth is unknown. We hypothesized that c-Myc, a master transcription factor/oncogene and regulator of both metabolism and growth, is central to this axis under conditions of metabolic stress.

METHODS

Metabolic stress was modeled in A549 cells exposed to mitochondrial inhibitors (EtBr, hypoxia, Sirtuin3-siRNA) or exposed to low-nutrients media; mitochondrial function was measured in the Seahorse platform; gene sequencing was performed by rapid amplification of cDNA ends (RACE) sequencing.

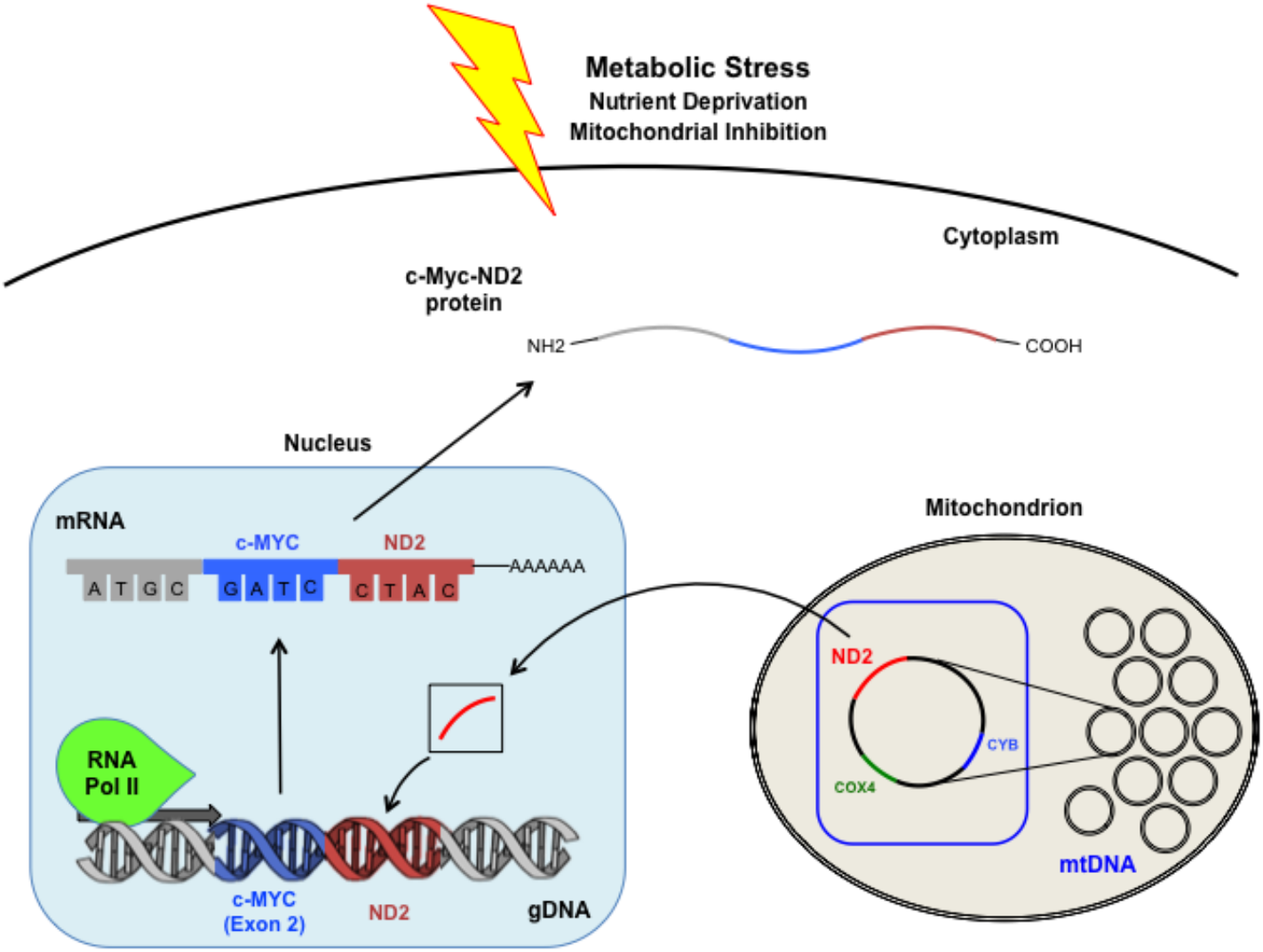
RESULTS

Mitochondrial inhibitors or low nutrient supply (low serum, glucose, methionine) induced (in a reversible manner) a distinct cytoplasmic c-Myc isoform with a size (70kDa) different from all described c-Myc isoforms. Preliminary sequencing (RACE) suggests that its mRNA is the product of a fusion between exon 2 of c-Myc and a sequence 100% homologous to a C-terminal segment of the mt-ND2 gene (encodes NADH dehydrogenase subunit 2 of the mitochondrial respiratory complex I). Since ND genes belong to mtDNA, the c-Myc-ND2 protein is likely the product of a “nuclear mitochondrial sequence” (NUMT). These rarely described examples of gene fusion have resulted from “gene jumping” of mitochondrial genes into nDNA early in evolution (Figure). c-Myc-ND2 was low/absent in normal cells but highly expressed in several cancers. siRNA-inhibition of c-Myc-ND2 increased proliferation (p-Rb, cyclin A levels) and glycolysis.

CONCLUSIONS

A novel c-Myc-ND2 fusion protein may act as sensor/mediator of metabolic stress. Its effects are opposite to those of c-Myc. A parallel regulation of the two proteins may control the response to metabolic stress in normal vs. cancer cells, exposing novel therapeutic targets.

Supervisor: Dr. Evangelos Michelakis


Metabolic Stress
Nutrient Deprivation
Mitochondrial Inhibition
Cytoplasm
c-Myc-ND2
protein
NH2
COOH
Nucleus
mRNA
c-MYC
ND2
A T G C
G A T C
C T A C
AAAAAA
RNA
Pol II
c-MYC
(Exon 2)
ND2
gDNA
Mitochondrion
ND2
CYB
COX4
mtDNA

Distinctive Functions of PI3Kβ in Endothelial Cells and Cardiomyocytes in Response to Myocardial Infarction: Complications for Targeting PI3Kβ in Myocardial Infarction Treatment

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

INTRODUCTION

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

METHODS

Mice with kinase-dead p110β expressed specifically in cardiomyocytes (p110β-αMHC) or endothelial cells (p110β-Tie2) were generated; p110β-Flx was used as littermate controls. Intraperitoneal injection of Tamoxifen (2mg/mouse for 5 days) was given to p110β-Tie2 to activate kinase-dead p110β expression. Sham- or MI-operation on mice was performed in a blinded fashion. Cardiac function was assessed by echocardiography and mortality data were collected. Post-MI remodeling processes, such as the infarct size, vascular density, hypertrophy, and apoptosis, were examined by specific methods. Signaling pathways were assessed by Western blotting.

RESULTS

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

CONCLUSIONS

Inhibition of endothelial p110β improves cardiac performance after MI through augmenting endothelial Akt activation, which highlights the potential of PI3Kβ inhibition in MI treatment. Conversely, cardiomyocyte p110β is required to maintain cardiac function following MI, indicating the importance of cell-type specific PI3Kβ regulation in heart diseases therapy.

Supervisor: Dr. Gavin Oudit

Serum Vitamin-D and Mental Health, a National Canadian study

Filmer Chu; Arto Ohinmaa; Scott Klarenbach; Paul Veugelers; Zing-wae Wong
Supervisor: Arto Ohinmaa

INTRODUCTION

Depression is responsible for the greatest proportion of disease burden attributable to non-fatal health outcomes worldwide. The main function of vitamin D is calcium homeostasis however, emerging evidence has correlated adequate levels of serum vitamin D with better mental health. Determining reversible factors that may reduce the disease burden may have important effect on health, productivity, and the cost of care.

METHODS

A cross-sectional survey representative of the Canadian population (Canadian Health Measures Survey) was used to determine the association between Serum Vitamin-D and depression. Three depression proxies and one generic health proxy were used, and each outcome independently investigated using ordered logistic regression models with increasing specificity that account for demographics, socio-economic status, physical activeness, chronic conditions, smoking and drinking, illicit drug use and labor force status. Margin effects are used to determine the probability of the average adult Canadian being in the best mental health state by serum vitamin-D levels. The best mental health state is defined as the respondent being in the healthiest mental health category.

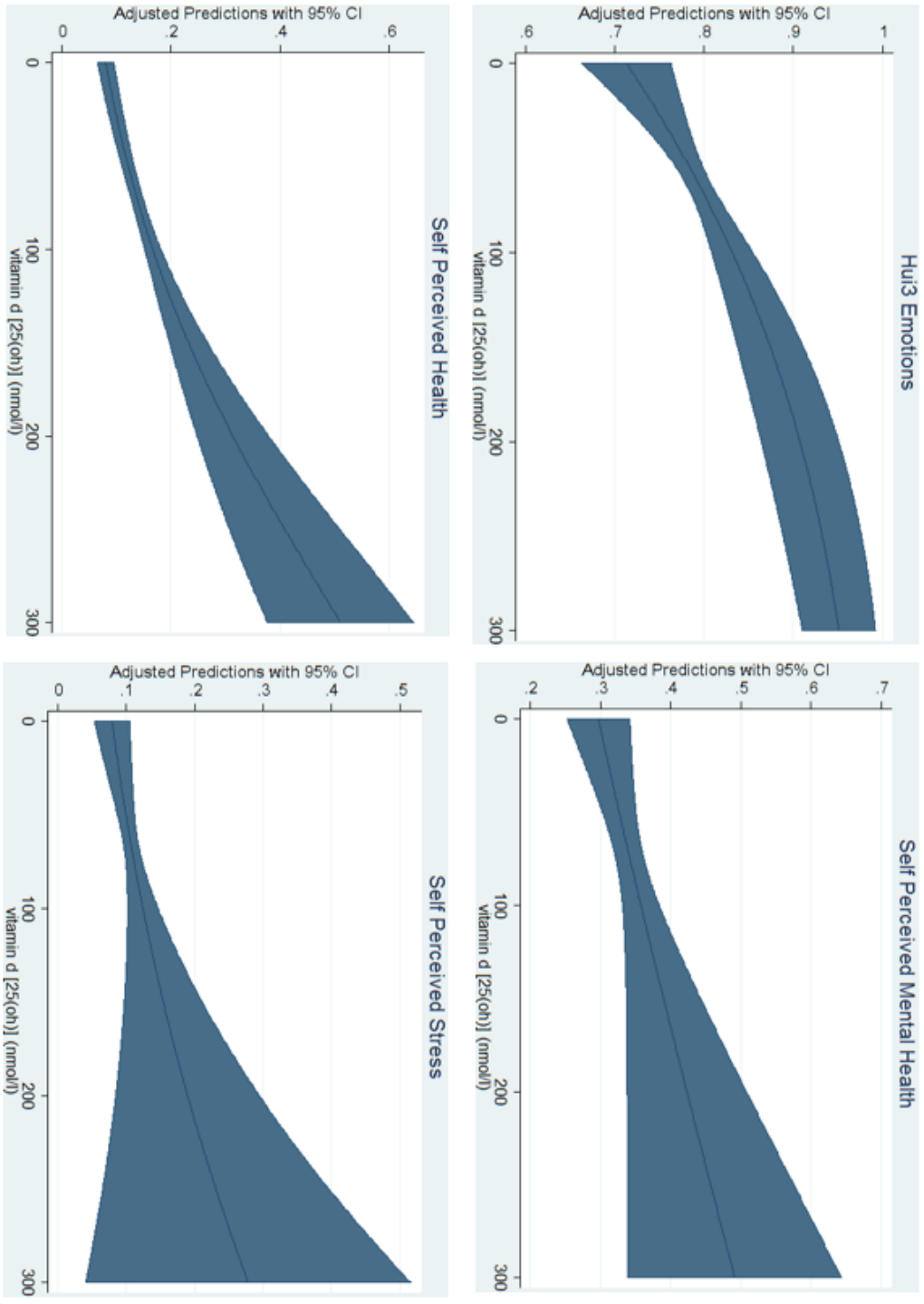
RESULTS

A positive robust association between serum vitamin-D levels and depression was found. For a one nmol/L increase of serum vitamin D in the blood stream, there is an average of a 1.01 increase in log odds of being in the best health state across all models. In the fully adjusted ordered logistic model, the probability of an average Canadian being in the best mental health and general health state increases with more serum Vitamin-D (Figure 1).

CONCLUSIONS

The actual cost of vitamin-d and potential harm from toxicity is low resulting in a cost-effective solution to lower the risk of mental health disorders at the population level. These results are similar to two previous Canadian studies utilizing an older sub-population, and are consistent with other studies found around the world.

Supervisor: Dr. Arto Ohinmaa


Adjusted Predictions with 95% CI
Hui3 Emotions
vitamin d [25(oh)] (nmol/l)
Adjusted Predictions with 95% CI
Self Perceived Health
vitamin d [25(oh)] (nmol/l)
Adjusted Predictions with 95% CI
Self Perceived Mental Health
vitamin d [25(oh)] (nmol/l)
Adjusted Predictions with 95% CI
Self Perceived Stress
vitamin d [25(oh)] (nmol/l)

Detecting ALS Pathology Using 3D Whole Brain Texture Analysis

Michael Chunn, Abdullah Ishaque, Daniel Ta, Sneha Chenji, Dennell Mah, Peter Seres, Herb Yang, Sanjay Kalra
Supervisor: Dr. Sanjay Kalra

INTRODUCTION

ALS pathology is heterogeneous and difficult to detect with standard MRI. Texture Analysis (TA) can detect statistical patterns of voxel intensities in MR images. The study of TA to detect cerebral degeneration in ALS has been limited to one whole-brain 3D study done using a 1.5T system, and one 2D ROI-based study. The current study aims to assess ALS degeneration with whole-brain 3D TA using a 3T dataset.

METHODS

Nineteen patients and fourteen healthy, age-matched controls (patients 57.1 ± 8.9 years, controls 56.3 ± 9.2 years) underwent T1-MPRAGE MRI scans. Images were in 1x1x1mm resolution, and were preprocessed using VBM8 in Matlab's SPM8 toolbox. Twenty-two texture features based on Gray Level Co-occurrence Matrix (GLCM) were extracted using the VGLCM TOP3D toolbox. Texture features were smoothed on a 3x3x3 kernel, and then compared between patients and controls with a two sample t-test, with age as a covariate. Statistical significance was accepted with a p-value of 0.001, with a threshold cluster size of 5.

RESULTS

Texture analysis revealed widespread changes in the brain in ALS patients when compared with controls. All texture features were significantly different between groups. Consistent changes were noted in the bilateral precentral gyri. Changes were present in both the grey and white matter of the frontal and temporal lobes. Several texture features distinctly highlighted the corticospinal tract as an area of abnormality. These are all areas where pathological changes have been previously noted in ALS patients. Figure 1 shows both positive and negative change in the texture feature value. Positive changes to GM often occurred adjacent to negative changes to WM, and vice versa – dependent on the texture feature in question.

CONCLUSIONS

Texture analysis was successful in detecting areas of known ALS pathology in motor and non-motor regions of the brain. Texture analysis is sensitive to both GM and WM pathology.

Supervisor: Dr. Sanjay Kalra

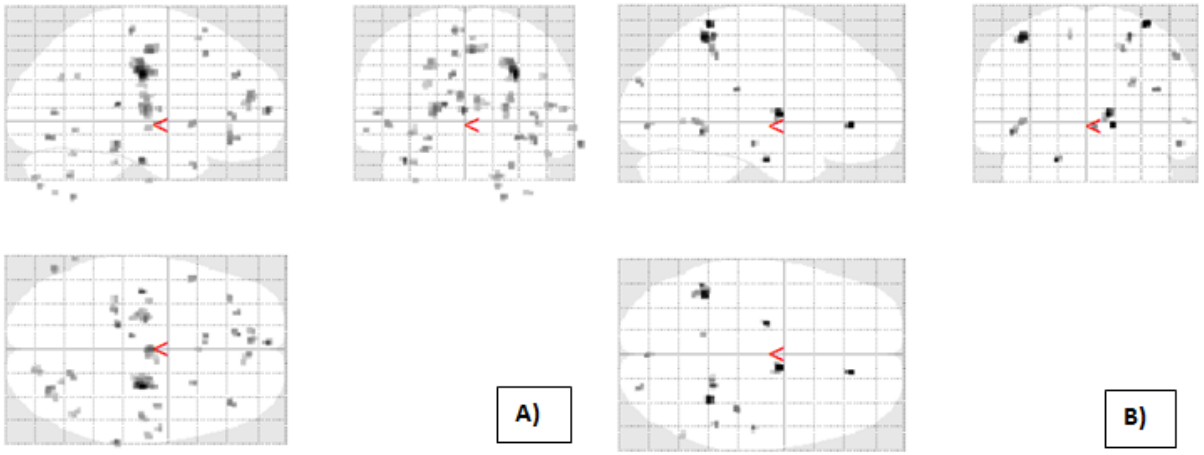


Figure 1. A) Positive change in texture feature *energ* visualized in a glass brain representation in Matlab. Changes are present in both the WM and GM in patients, most notably the right corticospinal tract. **B)** Negative change in texture feature value is visualized in Matlab's glass brain, with change visible in the somatosensory cortices.

Establishing a novel metabolomic biomarker detection technique for early exposure to welding fumes

Meghan Dueck, Sindhu Nair, James Mino, Marc Cassiède, Samineh Kamravaei, Pascal Mercier, Paul Shipley, David Broadhurst, Bernadette Quémerais, and Paige Lacy
Supervisor: Dr. Paige Lacy

INTRODUCTION

Welding is a crucial industry for construction and maintenance of infrastructure. With over 70 different welding techniques, those employed in the trade are exposed to a wide variety of hazardous fumes. Continuous respiratory exposure can lead to detrimental health effects. In this study, we used urinary metabolomics to screen for potential biomarkers for exposure to welding fumes. In addition, metal analysis was conducted to determine levels of urinary metals.

METHODS

Metal and particle mass concentrations were analyzed from welder and control air samples. Fasting urine samples were collected on days 0, 1, 7 and 50 of instructional programs at the Northern Alberta Institute of Technology (NAIT). Urinary metabolites and metal concentrations were analyzed using proton nuclear magnetic resonance (1H-NMR) and inductively coupled plasma mass spectrometry (ICP-MS), respectively, from male non-smoking participants (18-40 years) distributed into two groups: (i) 23 apprentice welders, and (ii) 20 non-welder controls. Pooled urine from 5 welders was used for quality control (QC) to determine reliable metabolites.

RESULTS

Air samples demonstrated that welder participants were exposed to significantly higher metal and particle concentrations than control subjects on days 1, 7 and 50 ($p < 0.0001$). A total of 151 metabolites were screened in samples, and 61 were validated as reliable (< 20% RSD) based on 34 QC samples. No differences between welder and control participants were found for metabolite and metal concentrations using RM-ANOVA; however, t-test analysis showed significant changes in several metabolites as well as urinary chromium on day 50.

CONCLUSIONS

Well-matched control and welder groups were obtained based on urinary metabolite and metal measurements on day 0. Following acute exposure to welding fumes, welders showed changes in urinary metabolites and metals compared with controls. Future studies will be directed at measuring the impact of long-term chronic welding fume exposure in full-time welders.

Supervisor: Dr. Paige Lacy

Comparison of Estimated Caloric Requirements in Cirrhotic Patients Using Prediction Equations versus Indirect Calorimetry: A Systematic review and Individual Participant Data Analysis

T. Eslamparast1, B. Vandermeer1, M. Raman2, V. Mathiesen3, D. Belland3, M. Ma1, P. Tandon1*
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Malnutrition is a common and among the leading cause of poor outcomes in cirrhosis. Dietary approach remains the mainstay of therapy. In practical setting, utilizing predictive equations to estimate resting energy expenditure (REE) and target caloric requirement as these are more time-efficient than gold-standard direct and indirect calorimetry is a common method. However, predictive equations are associated with over- and under-estimation of energy requirements. As accurate nutrition prescriptions are important in cirrhosis patient care, our aim was to compare the caloric requirements estimated using prediction equations (predicted REE, pREE) versus indirect or direct calorimetry measurements (measured REE, mREE).

METHODS

We included full-text English language studies on adults with cirrhosis comparing pREE versus mREE. Excluded studies had >20% of patients with hepatocellular carcinoma. Electronic databases were searched up to May 2016. Studies used either the Harris-Benedict equation for pREE or some variation thereof. A DerSimonian-Laird random-effects meta-analysis was used to pool the mean differences across studies. The intraobserver reproducibility of pREE was determined by intraclass correlation coefficient (ICC).

RESULTS

Our meta-analysis included 20 studies comprising 1883 patients. Among these studies, we were analyzed the induvial data of 7 studies. A total of 14 studies underestimated caloric requirements using the predictive equations. When pooled, the mean difference across studies was an underestimate of 75.9 (95% CI: 12.83-138.96) kcal/d. The pooled analysis was associated with significant heterogeneity (I2=93%, Fig 1).The pREE values showed a good correlation with mREE measurements. The absolute ICC of pREE measurements were 0.86, 0.83 and 0.83 for HB, Mifflin and schofield equations respectively.

CONCLUSIONS

Our results highlight the need to accurately define the subgroup of patients at risk for underestimation of caloric requirements and have them complete indirect calorimetry assessment.

Supervisor: Dr. Puneeta Tandon

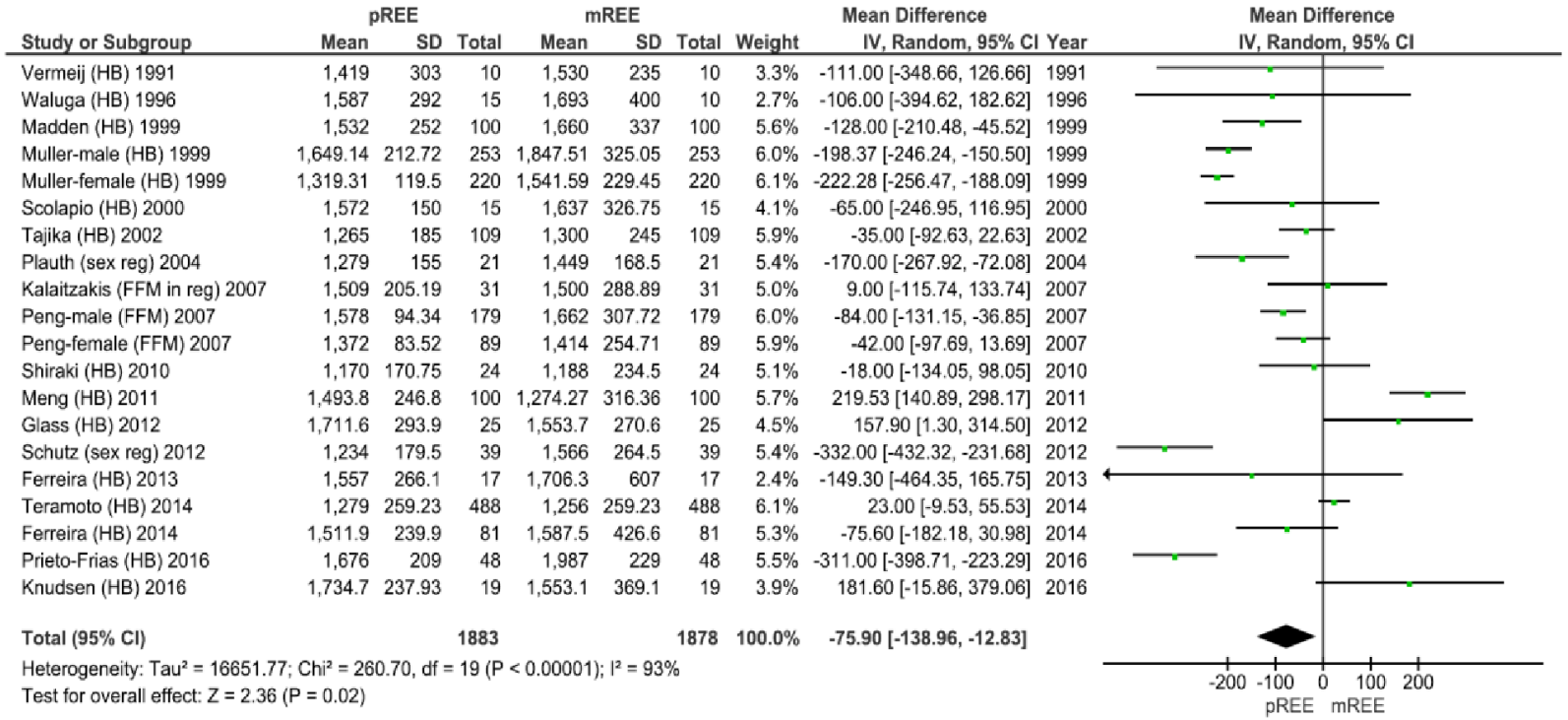


Fig 1. Forest plot of comparison: measured Resting Energy Expenditure (mREE) *vs.* predicted REE (pREE). Abbreviations in parenthesis show the predictive equations employed by each study (HB: Harris-Benedict, FFM & FFM in reg.: using the individual fat free mass in the linear regression equation derived from cirrhotic or control group, sex reg.: using gender specific regression equations derived from healthy population)

The utility of the SOFA score in discrimination of post-transplant survivors and recipients in critically ill cirrhotic patients: a multicentre cohort study

Amanda Ewasiuk (1), Thomas Lescot (2), Peter Goldberg (2), Michael D Sharpe (3), Juan J Ronco (4), Norman M Kneteman (5), Markus Selzner (6), Demetrios J Kutsogiannis (1), Sheela Maria Xavier (1) and Constantine J Karvellas (1,7)
Supervisor: Dr. Constantine Karvellas

INTRODUCTION
Liver transplantation (LT) in cirrhotic patients with evidence of organ dysfunction poses significant challenges. This study investigated the relationship between the Sequential Organ Failure Assessment (SOFA) and a) 90-day post-LT mortality in critically ill cirrhotics receiving LT and b) the likelihood of receipt of LT from ICU.

METHODS
Retrospective cohort study of critically ill cirrhotics (ICU) receiving LT (n=220) from 5 Canadian centres between January 2000 and December 2015 and all critically ill patients receiving liver transplant and those requiring ICU care who were listed, but died waiting for transplant (n=109) from 2 Canadian centres.

RESULTS
In critically ill cirrhotic patients receiving LT, compared to non-survivors (n=34), survivors (n=186) were significantly younger (53 vs. 56 years, p=0.0097). In LT recipients, mortality at 90 days was 15.5%. The most common etiology amongst survivors was hepatitis C (31%) and amongst non-survivors was alcoholic cirrhosis (29%). Multivariate analysis showed that age was independently associated with higher risk of 90-day mortality (OR 1.07 per year, 95% CI (1.02-1.13), p=0.009). Of patients listed for transplant (n=109), 44% died without receiving a LT. Multivariate analysis showed that a higher SOFA score was independently associated with decreased likelihood of receipt of LT at admission (OR 0.94, 95% CI (0.88-0.99), p=0.03) and at 48 hours (OR 0.85, 95% CI (0.79-0.92), p<0.0001).

CONCLUSIONS
In critically ill cirrhotics undergoing LT, increased age was independently associated with increased 90-day mortality post-LT. Higher SOFA score at admission and at 48 hours was independently associated with decreased likelihood of receipt of liver transplant in cirrhotics waiting in the ICU for LT.

Supervisor: Dr. Constantine Karvellas

Table 1. Independent associations with receipt of Liver Transplant from ICU in 246 critically ill cirrhotics listed for transplant

Covariate	Unadjusted (n=246)	p-value	Model 1 (n=232)	P	Model 2 (n=194)	P
Age	1.00 (0.97-1.02)	**0.79**	**0.99 (0.97-1.02)**	**0.5**	0.98 (0.95-1.02)	**0.3**
Gender (female)	1.09(0.63-1.87)	0.76	1.13 (0.64-2.01)	0.7	0.96 (0.51-1.83)	0.9
Etiology (HCV vs. non-HCV)	1.15 (0.66-2.00)	0.62	1.27 (0.71-2.26)	0.4	1.23 (0.64-2.35)	0.5
SOFA (admission)	**0.94 (0.89-0.99)**	**0.029**	**0.94 (0.88-0.99)**	**0.026**		
SOFA (48 hours)	**0.86 (0.80-0.93)**	**<0.0001**		0.026	**0.85 (0.79-0.92)**	**<0.001**
C-statistic (AUROC)			0.59		0.69	

Role of receptor interacting protein 2 in allergic airway inflammation

Yahya Fiteih, Shairaz Baksh and Harissios Vliagoftis
Supervisor: Harissios Vliagoftis

INTRODUCTION

Persistent NF-κB activation has been associated with allergic airway inflammation in asthma. Receptor interacting protein 2 (RIP2) is a serine /threonine kinase that has been implicated in NF-κB activation. RIP2 polymorphism has been associated with severe childhood asthma. Furthermore, RIP2 gene silencing attenuated airway inflammation and airway hyper-responsiveness in ovalbumin-induced mouse asthma model. However, the mechanism of RIP2-mediated airway inflammation is not fully understood. To further investigate the role of RIP2 in asthma we will explore the effect of inhibiting RIP2 in mouse model of asthma using a new selective inhibitor.

METHODS

Male Balb/c mice (6-8 weeks old) were sensitized twice with ovalbumin (10µg) + aluminium hydroxide (2mg) via intraperitoneal (i.p) injection and then challenged twice with ovalbumin (50µg) intranasally. A new selective RIP2 inhibitor (RIP2 inhibitor-1) designed by Dr. Baksh, was administrated once daily for 3 days during challenge (1µg/g body weight) via i.p injection. Mice were euthanized 24 hrs after the final challenge and bronchoalveolar lavage (BAL) fluid was collected. Airway inflammation was assessed by determining total and differential cell counts in BAL fluid. Lung tissues were collected for cytokine and chemokine analysis. Other mice were evaluated for airway hyper-responsiveness 24 hrs after the final challenge using Flexivent (SCIREQ).

RESULTS

There was significant decrease in the total number of cells and in the percentage of eosinophils in BAL fluid from mice treated with ovalbumin + RIP2 inhibitor -1 when compared to mice treated with ovalbumin only. RIP2 inhibitor -1 decreased the total number of cells in BAL fluid by 50.1% ± 17.33% and decreased the percentage of eosinophils in BAL fluid by 33.34 % ± 5.05%, n = 12 for all groups.

CONCLUSIONS

RIP2 inhibtor-1 attenuated airway inflammation in ovalbumin-induced experimental asthma. RIP2 inhibition may be a novel therapeutic approach for the treatment of asthma

Supervisor: Dr. Harissios Vliagoftis

Is Chronic Obstructive Pulmonary Disease really a risk factor for Coronary Artery Disease?

Yongzhe Hong, Michelle Graham, M. Sean McMurtry
Supervisor: Michael Sean McMurtry

INTRODUCTION

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

METHODS

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

RESULTS

There were 26,137 patients included in the analysis, with a mean age of 63.3 ± 12.2 years and 19542 (74.8%) of which were male. The crude odds ratio of having CAD was 0.83 (95% CI 0.74-0.92) for patients with COPD compared to those without COPD in univariate logistic regression analysis. After controlling for age, gender, smoking history, BMI and hypertension, diabetes, hyperlipidemia, peripheral artery disease, and cardiac family history it became 0.75 (95% CI 0.67-0.84).

CONCLUSIONS

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

Supervisor: Dr. Michael Sean McMurtry

Univariate and Multivariate logistic regression analysis

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

COPD, chronic obstructive pulmonary disease; BMI, body mass index.

A high sodium diet abolishes renal vascular conductance reduction in response to acute renal venous pressure elevation

Xiaohua Huang 1, Shereen Hamza 1,2, Wenqing Zhuang 1, William Cupples 3 and Branko Braam 1,2
Supervisor: Dr. Branko Braam

INTRODUCTION

Increased renal venous pressure (RVP) induced by systemic congestion is presumably an important mediator of worsening kidney function in cardiorenal syndrome. Kidney plays an essential role in maintaining sodium and water balance. The exposure of high sodium intake suppresses the renin-angiotensin system (RAS), potentially affecting the sodium handling upon increased RVP. In the present study, our hypothesis is that acute RVP elevation increases vascular tone leading to decreased renal vascular conductance (RVC) can be abolished by high sodium diet.

METHODS

39 male Lewis rats (300-400g) received a regular sodium diet (NS; n=24) or a high sodium diet 14 days (6% NaCl, HS; n=15). Before the experiments, animals were randomly assigned into 3 groups: time control, increased RVP to 10mmHg or to 20mmHg. Mean arterial pressure (MAP) and RVP were assessed using femoral artery and adrenal/spermatic vein catheters. GFR was measured by FITC inulin clearance. Left renal arterial blood flow (RBF) was measured by transit-time flow probe. To increase RVP, the left renal vein was partial occluded for 120 min.

RESULTS

High sodium diet or elevation of RVP did not alter MAP. Increased of RVP from 0.6±0.2 to 19.9±0.4 mmHg significantly decreased RBF (7.0±0.5 to 3.4±0.6 ml/min, $p<0.05$) and RVC (-0.03±0.01 ml/min.mmHg, $p<0.001$) in NS rats, but not in HS rats. Acute increases in RVP decreased ipsilateral GFR. The GFR reduction was more severe in NS than in HS rats (1.21±0.01 to 0.33±0.13 ml/min, $p<0.001$ vs 1.73±0.06 to 0.86±0.13 ml/min, $p<0.05$).

CONCLUSIONS

Acute elevated RVP induces an immediate reduction in RBF, RVC and GFR, which is ameliorated by high sodium intake. This suggests an important role for the RAS in the vasoconstriction induced by increased RVP, which could be relevant in congested states like renal disease and heart failure.

Supervisor: Dr. Branko Braam

Liquid biopsies using circulating DNA (ctDNA) as a new molecular diagnostic for cutaneous T cell lymphoma (CTCL)

Aishwarya Iyer1, Abdelbasset Hamrouni2, Dr. Robert Gniadecki1,2
Supervisor: Dr. Robert Gniadecki

INTRODUCTION

CTCL is a rare and uncommon type of non- Hodgkin's lymphoma. There are mainly two types of CTCL: Mycosis fungoides (MF) and Sézary syndrome (SS) that are derived from CD4+ skin-homing T cells. MF is the common form of CTCL that appears as scaly, itchy red rash or raised plaques. MF is slow growing, difficult to diagnose and often confused with other inflammatory skin diseases. SS is rare and more aggressive form of CTCL with lymphomas in skin, blood and lymph nodes. Even after diagnosis, there are no prognostic markers to predict if the disease would be slow growing or aggressive.

METHODS

T cell receptor (TCR) clonality is assessed by PCR using standard Biomed2 primers as a marker for CTCL diagnostic. The presence of dominant PCR fragment is considered as indication of T cell monoclonality. This method has proven to be important for CTCL diagnosis. However, the actual VDJ sequence remains unrecognized with this diagnostic method. This can be misleading as different VDJ sequence with same length of PCR fragment would means different TCR clones. As histopathology and molecular diagnostics is insufficient to diagnose all MF/SS cases, we propose using ctDNA from plasma/serum to amplify TCR specific sequencing and identify the different VDJ recombination sequences using next generation sequencing (NGS).

RESULTS

The amplification of different TCR sequences (γ/δ and α/β) is done using traditional PCR and linker mediated PCR (LM-PCR).

CONCLUSIONS

The LM-PCR protocol is developed to amplify the TCR sequences from fragmented DNA found in plasma/serum, as the traditional PCR might not amplify these shorter sequences.

Supervisor: Dr. Robert Gniadecki

GCSF in Allogeneic Clinical Islet Transplantation is not Associated with Improved Long Term Graft Survival

A. Lam (1,2), S. Imes (2), A. Malcolm (2), J. Shapiro (2,3), P. Senior (1,2)
Supervisor: Dr. Peter Senior

INTRODUCTION

Granulocyte colony stimulating factor (GCSF) is routinely used to treat neutropenia in clinical islet transplant (CIT) recipients. Recent recognition of GCSF as a regulator of T cell responses has led to interest in the potential of GCSF to improve cell survival. Indeed, retrospective studies in CIT suggest improved islet graft survival in subjects receiving GCSF and exenatide . Additionally, the combination of anti-thymocyte globulin (ATG), a potent lymphodepleting (LD) agent, and GCSF has preserved cell function in new onset type 1 diabetes (T1D). This study was performed to determine the effect of GCSF alone on islet graft survival and whether this effect is influenced by the use of LD agents for induction.

METHODS

We retrospectively analyzed data from 164 patients with T1D who underwent CIT at our institution between 1999-2015. Immunosuppression induction included LD agent (ATG or alemtuzumab, n=84) or non-LD agent (daclizumab, n=80).

RESULTS

Graft survival (C-peptide > 0.1 nmol/L) from first CIT was 6.6 + 0.4 years (mean + standard error). 47 patients were treated for neutropenia with GCSF for a median total dose of 900 mcg (300 – 9600 mcg). GCSF treatment did not significantly affect graft survival (hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.28-1.73, p=0.41). Furthermore, graft survival was not different with GCSF treatment when an LD agent (HR 0.98, 95% confidence interval (CI) 0.23-4.10, p=0.97) or a non-LD agent (HR 0.61, 95% CI 0.18-2.10, p=0.44) was used for induction.

CONCLUSIONS

The data presented here represents the largest reported cohort of CIT patient who have received GCSF and our retrospective analysis shows that GCSF treatment alone (without exenatide) is not associated with improved long term graft survival. Our results do not preclude further prospective studies of GCSF in CIT, but suggest that patient selection, timing and dose of GCSF be carefully considered in the study design.

Supervisor: Dr. Peter Senior

Microarray Analysis of Patient Outcomes in Ulcerative Colitis

Katelynn S. Madill-Thomsen, Vojislav Jovanovic, Jeff Reeve, Simone Withecomb, Philip F. Halloran, Brendan P. Halloran.
Supervisor: Dr. Philip F. Halloran

INTRODUCTION

There is an unmet need for improved diagnostic and prognostic methods in ulcerative colitis (UC). Current standards include the Mayo Score, fecal calprotectin, and histology, but these do not necessarily correlate strongly with disease course and outcomes. Kappa values for endoscopic mayo scoring between experts is at best only fair (range 0.53-0.71)[1]. Gene expression microarray analysis of transplant biopsies using the Molecular Microscope Diagnostic System (MMDx) has shown promise for predicting response to therapy and patient course [2]. We hypothesized that this novel approach could also be applied to UC colonic biopsies.

METHODS

Microarrays were used to measure global gene expression in 43 for-cause UC colon biopsies. Resulting “CEL” files and associated clinical data (demographics, clinical and endoscopic phenotype) were analyzed using the R programming language. CD55 was selected for analysis, along with the pathogenesis-based transcript sets (PBTs, http://atagc.med.ualberta.ca/Research/GeneLists/Pages/); QCATs, QCMATs, GRITs, IRRATs, CT1s, CT2s, and molecular calprotectin (mCalpro, S100A8 and S100A9)[3]. The associations between these genes/gene sets and two definitions of clinical outcome in UC patients were assessed (Table 1).

RESULTS

P-values for associations with the Endoscopic Mayo Outcome and Future Treatment Course are given in Table 2 (one tailed t-tests). All selected PBTs and CD55 were significantly (p-value ≤ 0.05) different between Mayo score ≤ 1 and >1 patients. All PBTs and CD55 also distinguished ‘mild course’ patients from ‘moderate’, or ‘severe course’. CD55, however, separated all three categories with statistical significance, suggesting potential utility as a prognosticator (Figure 1).

CONCLUSIONS

These data show significant associations between molecular scores and patient course, suggesting that molecular assessments are a useful predictor for clinical and endoscopic outcomes. Microarray analysis offers a reproducible and granular method for prognosis and diagnosis. Thus, MMDx opens the door to a new objective test that will change patient care.

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1. Dig Liver Dis. 2014 Nov; 46(11): 969-973
2. Nat Rev Nephrol. 2016 Sep; 12(9): 534-548
3. Inflamm Bowel Dis. 2014 Dec; 20(12): 2353-2363

Supervisor: Dr. Philip F. Halloran

Table 1. Clinical outcome category patient assignment descriptions		
Outcome Category	**Assignment**	**Clinical Description**
Endoscopic Mayo Outcome	0	Follow-up scope with endoscopic mayo score of 0-1
	1	Follow-up score with endoscopic mayo score of 2-3
Future Treatment Course (clinical course description)	0	Mild course, patient doing well, no changes, excellent disease course.
	1	Moderate course, one moderate event (new biologic, dose escalation of biologic or prednisone only, new immunosuppressant)
	2	Severe course, IBD related hospitalization, surgery, 2nd biologic initiated for treatment failure, need for steroid and biologic simultaneously to induce remission

Table 2. P-values* for associations (two-sample t-tests) between Outcome Categories and selected molecular microscope diagnostic (MMDx) scores).

Selected Genes and PBTs		Description	Endoscopic Mayo Outcome	Future Treatment Course		
			p-value	p-value (0vs1)	p-value (0vs2)	p-value (1vs2)
Genes	**CD55**	Cromer blood group system	0.03	0.0006	0.000003	0.02
PBTs	**QCAT**	T cell burden	0.004	0.007	0.02	0.61
	QCMAT	Macrophage burden	0.037	0.008	0.009	0.20
	GRIT	Interferon γ inducible transcripts	0.007	0.0002	0.0008	0.28
	IRRAT	Injury and repair response	0.045	0.004	0.0009	0.15
	CT1	Colon transcripts 1	0.043	0.003	0.006	0.30
	CT2	Colon transcripts 2	0.036	0.005	0.006	0.29
	mCalpro	Calprotectin expression in tissue, S100A8 and S100A9	0.029	0.001	0.0005	0.08

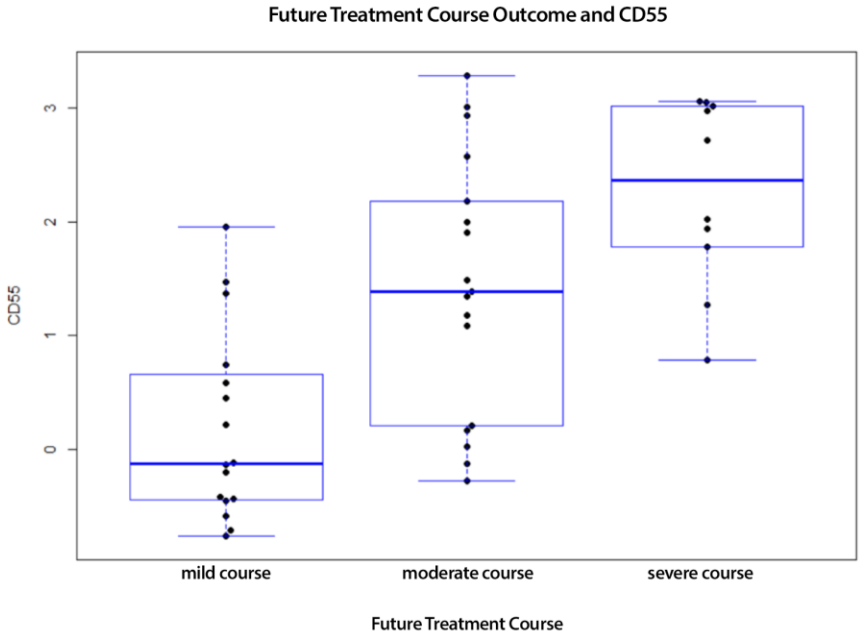

Figure 1. *CD55 separating mild patient course (no events, moderate patent course (1 moderate event), and severe patient course (1 severe event or >1 moderate event).*

Trends in admission rates and in-hospital stay for venous thromboembolism

Sola Mansour, Ghazi Alotaibi, Cynthia Wu, Michael Sean McMurtry
Supervisor: Dr. Michael Sean McMurtry

INTRODUCTION
Acute venous thromboembolism leads to significant morbidity and mortality. Advances in pharmacotherapy facilitate outpatient care in low-risk acute venous thromboembolism. The proportion of hospitalized acute venous thromboembolism cases and the average length of stay are not known. We sought to identify predictors of hospitalization, changes in hospitalization rates and length of stay of acute venous thromboembolism over a decade in Alberta, Canada.

METHODS
Using linked administrative health databases, we identified adult patients diagnosed primarily with acute venous thromboembolism between April 2002 and March 2012. We measured trends using Poisson regression, adjusted length of stay using analysis of covariance. We identified predictors of hospitalization using multivariate logistic regression.

RESULTS
8,198 out of 31,656 acute venous thromboembolism cases were hospitalized. The overall venous thromboembolism admission rates ranged between 23.7% and 27.8% with no evident temporal trend (P=0.10). The average admission rate was 51.9% for pulmonary embolism and 16.1% for deep vein thrombosis. The mean length of stay for deep vein thrombosis and pulmonary embolism remained unchanged with an adjusted mean for venous thromboembolism of 6.9±1.0 days. Higher Charlson index, older age, male gender, pulmonary embolism at presentation and multiple comorbidities were associated with hospitalization. Hospitalization was associated with 30-day mortality (odds ratio:2.8, 95%CI: 2.2-3.5) whereas the length of stay was not (odds ratio:1.0, 95%CI: 0.99-1.0).

CONCLUSIONS
Hospitalization rates and mean length of stay for acute venous thromboembolism did not change significantly between 2002 and 2012. Advances in pharmacotherapy have not yet reduced hospitalization rates or length of stay for venous thromboembolism.

Supervisor: Dr. Michael Sean McMurtry

Cardiac surgery in cirrhosis: a retrospective cohort study

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Supervisor: Dr. Constantine J. Karvellas

INTRODUCTION
Patients with cirrhosis and concomitant coronary/valvular heart disease present a clinical dilemma. Cardiac surgeons often are reluctant to operate in this high-risk population, potentially diminishing survival/potential for liver transplant. This study aimed to identify associations between the severity of cirrhosis and post-cardiac surgical outcomes.

METHODS
Retrospective cohort analysis of all patients undergoing cardiac surgery at the University of Alberta Hospital from January 1992 to July 2012 with an underlying diagnosis of cirrhosis prior to cardiac surgery (n=74). The relationship between severity of liver disease, medical comorbidity and surgical factors on survival to hospital discharge was evaluated.

RESULTS
Among 74 subjects, in-hospital mortality was 36%. Median Modified End-stage Liver Disease (MELD) score in the overall cohort was 11 (8-19). In comparing survivors (n=47), non-survivors (n=27) were older (mean 57 vs 49 years) and were more likely to have alcoholic cirrhosis (37% vs 17%, p=0.05 for both). Non-survivors were more likely to have ascites (41% vs. 17%, p=0.02), higher mean Charlson Comorbidity Index (CCI, 3.4 vs 2.0, p=0.0005), and also higher median creatinine (108 vs. 82 µmol/L, p=0.008) and MELD scores (14 vs 10, p=0.12; trend). Non-survivors underwent more valve procedures (44% vs 29%, p=0.20) although not significant. Non-survivors had longer median lengths of stay in ICU (9 vs 5, p=0.002) and in hospital (32 vs 11, p=0.0001) and were more likely to be on renal replacement therapy (37% vs 4%), p=0.0002) post-surgery. After adjusting for covariates (multivariable logistic regression), increased CCI was independently associated with increased mortality (Odds Ratio 1.78 per unit (95% CI 1.24-2.54), p=0.002).

CONCLUSIONS
Among cirrhotic patients undergoing cardiac surgery, mortality rates were high (36%). Non-survivors had more complications of liver disease (ascites, AKI) and medical comorbidity (CCI) prior to surgery and required more medical services and organ support post-operatively.

Supervisor: Dr. Constantine J. Karvellas

Characterization of vascular endothelial repair of Apelin-deficient hearts in Chronic Allograft Vasculopathy model in Mice

Andrew Masoud, Maikel Farhan, Gavin Y. Oudit and Allan G. Murray
Supervisor: Dr. Allan G. Murray

INTRODUCTION

Heart transplantation is a lifesaving treatment for end-stage cardiac patients. Long-term cardiac allograft survival is limited by chronic allograft vasculopathy (CAV), hence, CAV is a leading cause of mortality beyond the 1st year of transplantation. Immune injury targets the endothelial cells (ECs) lining the coronary arteries and microvasculature. The maladaptive repair response results in obliterative arterial intimal expansion, and microvessel injury. In turn, a decreased blood supply contributes to graft failure.

Apelin is an EC-specific protein, coded on the X chromosome that participates in vascular repair from myocardial infarction and kidney glomerular microvasculature injury. We hypothesize that Apelin-dependent pro-angiogenic signals are exploited for repair of CAV injury.

METHODS

CAV was induced via transplantation of male mouse hearts into female recipients to elicit a HY-minor histocompatibility antigen-directed, cell-mediated allo-immune response against the male donor hearts. Apelin-/y (knockout; KO) or Apelin+/y (wild type; WT) hearts were transplanted into WT female recipients. The heart grafts were harvested two or six weeks after transplantation. We characterized intima area, and endothelial loss in medium to large-sized arteries, inflammatory cellular infiltration, and microvasculature density, using Immunohistochemistry.

RESULTS

Apelin-/y donor hearts show an increase in circumference area of endothelial loss (1.4 ± .1 vs 0.4 ± .1%; 1.9 ± 0.2 vs 0.5 ± 0.1%; $P<0.05$), and intima expansion (Fig 1A) in conduit arteries at 2 and 6 weeks respectively. Further, Apelin-/y donor hearts have decreased microvessel density at 2 and 6 weeks (Fig 1B). An enhanced inflammatory cellular infiltration is observed in Apelin-/y donor hearts compared to controls (Fig 1 C, D).

CONCLUSIONS

Loss of Apelin exacerbates CAV, loss of microvessel density, and is associated with an enhanced inflammatory infiltrate evident at an early (2 week) timepoint after transplantation.

Supervisor: Dr. Allan G. Murray

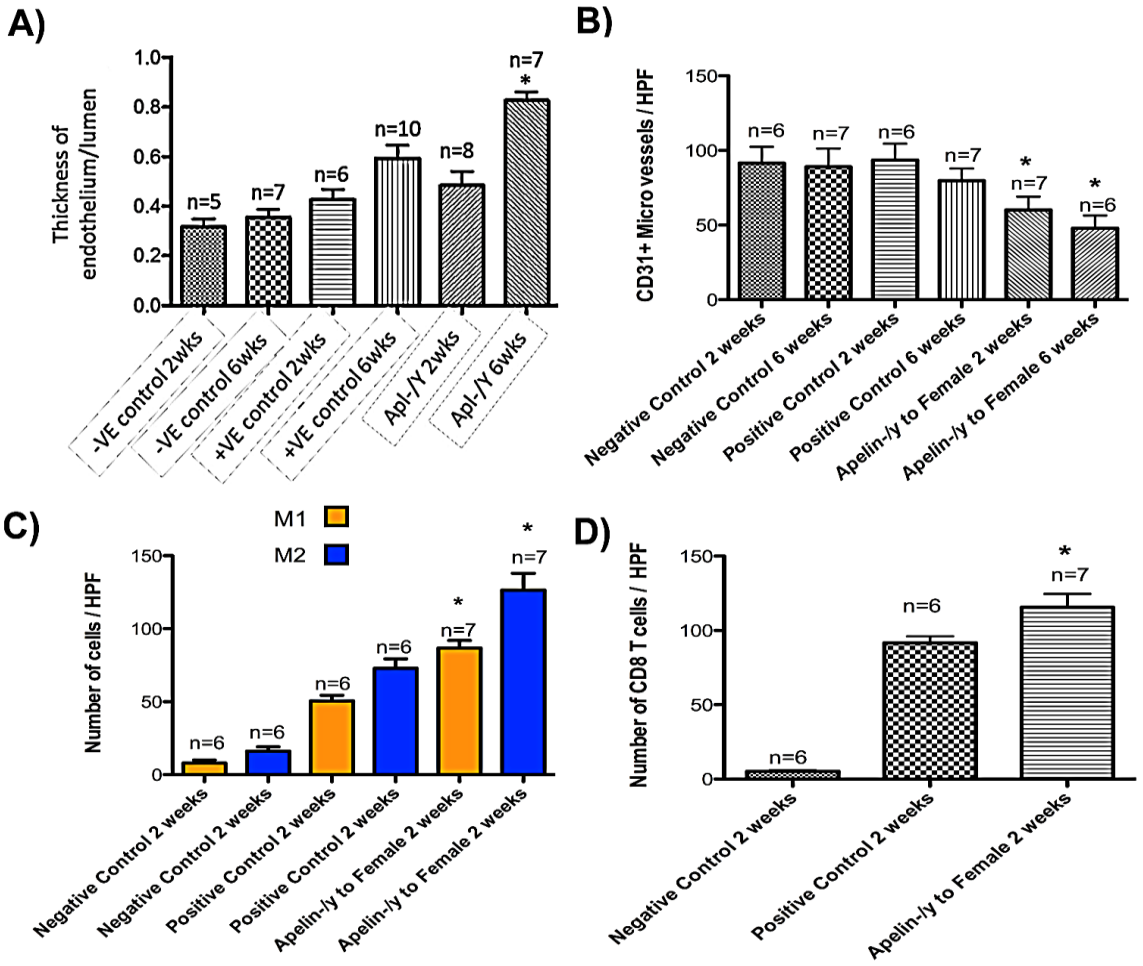

Figure 1. Histological analysis of heart transplants. A) Intima thickness of conduit arteries, B) microvessel density, C) macrophage infiltration, D) $CD8^{+}$ lymphocyte infiltration among $Apelin^{-/y}$ vs WT donor hearts at 2 and 6 weeks post transplantatiuon. (* = $p < 0.05$ vs control by ANOVA).

Protective Effect of Mast Cells in Co-Culture with Epithelial Cells when Exposed to Influenza A

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Supervisor: Dr. A. Dean Befus

INTRODUCTION

The role of mast cells (MC) in host defences against influenza A virus (FluA) is incompletely understood. We found that MC were resistant to productive FluA infection and suppress viral propagation in airway epithelial cells (AEC) in co-culture systems. We hypothesized that MC interact with AEC to produce a factor(s) that enhances anti-viral capabilities, therefore reducing viral replication and shedding of infectious particles and enhancing AEC survival.

METHODS

Our experimental model to investigate MC and AEC interaction during FluA infection involves a co-culture system with AEC (Calu-3) cultured on the membrane insert in the top chamber, and human MC (LAD2) in the bottom chamber. FluA infection was achieved by exposing AEC to A/PR/8/34 (H1N1; 0.04 MOI [multiplicity of infection]). Hemagglutination assay was used to assess viral propagation 3 days post infection. Multiplex system assay and ELISAs were used for candidate mediator detection, with commercially available antibodies to investigate inhibition of candidate chemokines. Supernatants of post-FluA experienced AEC-MC co-cultures were collected for further investigation. Fractionation of supernatants were performed using Centricon size exclusion filters (10kDa, 30kDa, 50kDa). Supernatants were treated to 65°C and 100°C for 30 minutes to investigate heat lability of anti-viral activity.

RESULTS

In the presence of MC, AEC were found to release 3-fold less FluA particles. A candidate mediator approach suggested CCL-4 to be of interest but inhibitory antibody did not suppress antiviral activity. Supernatant from a FluA experienced AEC-MC co-culture exhibits a protective effect against FluA in AEC. Fractionation approaches suggest that the soluble factor of interest is between 10kDa and 50kDa. Heat treatment of the supernatant suggest that the factor(s) is sensitive to 100°C but not 65°C.

CONCLUSIONS

FluA experienced co-culture supernatants have anti-viral activity mediated through a soluble factor(s) against FluA infection in AEC. Identification of the anti-viral factor(s) may foster novel approaches to enhancing FluA vaccination strategies.

Supervisor: Dr. A. Dean Befus

A National Surveillance Project on CKD Management in the Canadian Primary Care: Overview and representativeness

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Supervisor: Dr. Aminu Bello

INTRODUCTION

Although healthcare is provincially/territorially administered in Canada, existing national networks such as the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) are facilitators for the conduct of nationally-based quality improvement (QI)-based studies to improve chronic kidney disease (CKD) care.

OBJECTIVES

1) Determine the current practice pattern on risk identification and process of care for CKD based on established quality indicators, and 2) investigate the care variation across patients and provider 'demographics, and regional characteristics.

METHODS

The CPCSSN is the first pan-Canadian multi-disease surveillance system (collects health information from the primary care EMRs in eight provinces and one territory). The data repository contains health information on 1.5 million Canadians. The current initiative is targeted to including CKD in the list of chronic conditions for surveillance.

RESULTS

The CPCSSN database was used to develop a cohort of CKD patients being managed in primary care between January 1, 2010 and December 31, 2015. In this cohort, we identified 3,060,836 and 534, 823 available serum creatinine and urine albumin measurements respectively. There were ~381,000 urine albumin measurements in individuals with diabetes compared to ~154,000 measures in those without diabetes. The availability and spread of the measures of kidney function (serum creatinine) and albuminuria that defined CKD are comprehensive across multiple timeframes and disease conditions.

CONCLUSIONS

To our knowledge, this represents the largest Canadian cohort to estimate the burden and quality of care of CKD care in primary care. The coverage and representativeness of the measures for CKD appears high and represents a huge opportunity for understanding the current practice pattern in CKD management. This has implications on closing the gap between observed and expected burden and risks of CKD, and mapping the standard of care achieved, thereby providing opportunities for focused and effective population-level QI initiatives to enhance CKD care in Canada and beyond.

Supervisor: Dr. Aminu Bello

Table: Distribution of CKD measures overall, and by diabetes and hypertension status across time*

Reported eGFR < 60ml ml/min:	**Total**	**Diabetes**	**Hypertension**
At least 1 measurement at any time point	65,019	18,557	36,991
At least 1 measurement and this is the only one ever taken	8,369*	1,454	3,477
At least 2 measurements at any time point	41,084	13,859	26,242
At least 2 measurements 3 months apart, most recent in last 1 years	28,760	10,377	18,884
At least 2 measurements 3 months apart, most recent in last 2 years	34,967	11,971	22,537
At least 2 measurements 3 months apart, most recent in last 3 years	37,691	12,749	24,206
At least 2 measurements 3 months apart, most recent in last 4 years	39,325	13,273	25,191
Urine ACR >2.5mg/mmol:			
At least 1 measurement at any time point	32,885	22,508	21,115
At least 1 measurement and this is the only one ever taken	9,127	4,334	5,374
At least 2 measurement at any time point	17,400	13,489	11,771
At least 2 measurement 3 months apart, most recent in last 1 year	10,389	8,249	6,967
At least 2 measurement 3 months apart, most recent in last 2 years	13,516	10,712	9,060
At least 2 measurement 3 months apart, most recent in last 3 years	15,119	11,887	10,175
At least 2 measurement 3 months apart, most recent in last 4 years	16,012	12,498	10,794
Urine Albumin Concentration >20mg:			
At least 1 measurement at any time point	23,932	16,589	15,305
At least 1 measurement and this is the only one ever taken	5,968	2,854	3,553
At least 2 measurement at any time point	11,930	9,506	8,080
At least 2 measurement 3 months apart, most recent in last 1 year	4,289	3,511	2,960
At least 2 measurement 3 months apart, most recent in last 2 years	7,972	6,576	5,309
At least 2 measurement 3 months apart, most recent in last 3 years	9,797	7,977	6,575
At least 2 measurement 3 months apart, most recent in last 4 years	10,684	8,593	7,196

ACR=albumin: creatinine ratio. eGFR=estimated glomerular filtration rate.

*This table is based on lab-provided eGFR measurements. However, some labs provide creatinine measurements without recorded eGFRs measurements. For analysis purposes, we will calculate eGFR measurements from creatinine measurements. We anticipate the numbers in this table to increase when these calculations are made.

Assessment of BP Control in Hypertensive Remote-dwelling Patients with CKD

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Supervisor: Dr. Aminu Bello

INTRODUCTION

Chronic disease care in remote-dwellers with CKD is suboptimal, and degree of blood pressure (BP) control in this patient population is less clear. We hypothesized that the burden of uncontrolled BP is higher in remote-dwellers with CKD, and that living in a remote area is an independent predictor of uncontrolled BP status.

METHODS

We conducted retrospective chart review of a select group of patient population (history of CKD and hypertension) followed up for at least one year under the Northern Alberta Renal Program (NARP) Outpatient Clinics (N=320), from January 1, 2010 to December 31, 2015. Demographic, clinical and laboratory data were obtained through a review of anonymized medical records. The Kidney Disease Improving Global Outcomes (KDIGO) BP target definitions were applied in evaluating study outcomes. We performed univariate and multivariate logistic regression analyses to identify the significant determinants of uncontrolled hypertension.

RESULTS

Of the total participants, the prevalence of uncontrolled BP was 68%. In multivariate analysis, male sex (Odds ratio [OR], 2.5;95% confidence interval, 1.1.-5.5), and location of residence (remote/rural), OR, 2.6; 95% CI, 1.1-6.7) were independently associated with uncontrolled BP status. There was a significant association between increasing number anti-hypertensive drugs and uncontrolled BP by location (rural vs urban residence). The proportion of patients that required ≥ 4 classes of anti-hypertensive drugs to control BP was higher among the remote-dwellers compared to the urban dwellers (83% vs 17%, $p = 0.08$).

CONCLUSIONS

Prevalence of uncontrolled BP was higher in remote/rural-dwelling individuals with CKD and hypertension. Male sex and rural/remote residence were the independent predictors of uncontrolled BP in this patients' population, and remote-dwelling patients tended to require a higher number of medications to control BP as compared to the urban dwellers. These findings represent opportunities for improvement of CKD care amongst patients living in rural/remote communities.

Supervisor: Dr. Aminu Bello

Carotid chemoreceptor control of cardiovascular function at rest in COPD

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Supervisor: Dr. Michael Stickland

INTRODUCTION

COPD patients have increased sympathetic nerve activity and central arterial stiffness, both of which are linked to cardiovascular deterioration, and increased mortality. We have recently demonstrated enhanced activity/sensitivity of the carotid chemoreceptor (CC) in COPD which contributes to increased sympathetic nerve activity and peripheral arterial stiffness. Thus, the CC may play an important role in cardiovascular regulation in COPD. We hypothesized that CC inhibition would reduce central arterial stiffness and improve cardiovascular function in COPD.

METHODS

Thirteen non-hypoxemic mild-moderate COPD patients (mean FEV1±SD: 84±13% predicted) and twelve risk-matched controls completed 1) cardiopulmonary exercise test, 2) CC activity/sensitivity assessment and 3) resting cardiovascular function measurements with either intravenous (I.V.) saline or low dose I.V. dopamine (2 mcg/kg/min) while breathing normoxia or 100% O_2. Ventilation was evaluated by expired gas data and central arterial stiffness was determined by pulse wave velocity (PWV). Brachial blood flow was determined using Doppler ultrasound, cardiac output was estimated by impedance cardiography, and vascular conductance was calculated as flow/mean arterial pressure (MAP).

RESULTS

CC inhibition using either hyperoxia or dopamine decreased ventilation ($p<0.05$) in COPD, while no change was observed in controls. Central PWV and MAP were reduced with dopamine in COPD ($p<0.05$), but not with hyperoxia. No change in central PWV or MAP was observed in controls between conditions. Vascular conductance increased with dopamine in COPD ($p<0.05$) secondary to a reduction in MAP ($p<0.05$), while no change with dopamine was observed in controls. Hyperoxia had no effect on conductance or MAP in either group.

CONCLUSIONS

CC inhibition with dopamine improved conductance in COPD, suggesting that the CC is active at rest in COPD and contributes to tonic vasoconstrictor outflow.

Supervisor: Dr. Michael Stickland

Characterization and Comparison of Antibodies to Calcium Binding Protein – Spermatid Specific 1 (CABS1) in Studies of Human Submandibular Gland (hSMG) Extracts

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Supervisor: A. Dean Befus

INTRODUCTION

CABS1 appears to be a stress biomarker. Various molecular weight (MW) forms of CABS1 are present in hSMG extracts and saliva, with some appearing to predict resilience to stress. We hypothesize that following stress, CABS1 is processed into different molecular forms with distinct physiological effects. We propose to characterize MW forms of CABS1 detected with two antibodies and investigate their potential associations with stress.

METHODS

Two rabbit polyclonal antibodies against CABS1 were studied; immunogens from: aa 375-388 (‘H1’ antibody) and aa 184-197 (‘H2’). hSMG was homogenized and one of two protease inhibitor (PI) cocktails was added to the lysate to prepare extracts, and for comparison of the banding patterns using Western Blots (WB). Controls (no primary antibody, pre-immunization serum, blocked primary antibody) were ran in parallel.

RESULTS

CABS1 bands detected using ‘H1’ or ‘H2’ were analyzed and the MW of the polypeptides was determined. Five bands were regularly detected using ‘H1’ antibody; MW=28, 46, 57, 100, 205 kDa, whereas with ‘H2’ four bands were routinely detected: MW= 111, 75, 56, 33 kDa.
When using ‘H1’, one PI consistently conserved a lower molecular band (~25-28 kDa), whereas the other was unable to do so.

CONCLUSIONS

WB controls, together with Mass Spectrometry, suggest that the observed H2-immunoreactive bands are CABS1. Further confirmation is needed to see if some H1-immunoreactive bands are the same as those detected by ‘H2’. The protective PI mixture will be used routinely in the future. Since saliva is an easily obtained sample and CABS1 is present in saliva, we will characterize CABS-1 banding patterns in saliva and investigate if there is an association between stress and CABS-1 expression.

Supervisor: Dr. A. Dean Befus

mRNA methylation on 6-Adenosine selectively enhances translation of pre-existing stress response transcripts to mediate a timely and efficient response to stress

Bruno Saleme, Aristeidis Boukouris, Gopinath Sutendra, and Evangelos Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

RNA, the origin molecule of life, is categorized into rRNA, which forms the ribosome, tRNA which transfers amino acids, and mRNA, the template for protein translation. Methylation of Adenosine 6A is present in <1% of RNAs, but its role remains elusive. We speculated that translation of proteins critical for acute response to major stress is prioritized and amplified, to optimize a timely response to threat. We hypothesized that RNA methylation of selected RNAs allows prioritized translation of Stress Response Proteins (SRPs), like chaperones and transcription factors p53 and ATF4, under major stress, i.e. DNA damage or nutrient starvation

METHODS

RNA Dot blots, western blots, qRT PCR, immunofluorescence, mRNA immunoprecipitation performed in human cell lines (A549, HFF-1) exposed to UV, DNA damaging agents or nutrient/serum starvation.

RESULTS

Cells exposed to acute (0-4h) stress with UV irradiation or nutrient (serum, glucose, methionine) deprivation, exhibit a large increase in the methylation of rRNA and/or tRNA, but not mRNA. p53 and ATF4 are induced within minutes of the stress, independent of transcription (protein, but not mRNA levels, increased) which was not affected by proteasome inhibition. This suggests that translation of pre-existing mRNA causes the induction of these SPRs, which was diminished when mRNA methylation was inhibited via siRNA knockdown of mRNA methyltransferases. Translation of non-stress responsive proteins, such as actin, remained unaffected. Finally, apoptosis increased in cells with inhibited mRNA methyltransferases, suggesting an impaired response to stress.

CONCLUSIONS

While the importance of differential methylation of RNAs is yet to be determined, the fact that inhibition of mRNA methylation prevents the translation of SPRs and the ability of cells to handle stress, suggests that this may be a previously unrecognized but fundamental feature of cellular stress response. The implications of this work are wide and include diseases where major stress (like acute ischemia) can be catastrophic within minutes.

Supervisor: Dr. Evangelos Michelakis

Differential Regulation of p53 by Pyruvate Kinase M2 can be Therapeutically Targeted in Chemotherapy-Induced Cardiotoxicity

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Supervisor: Dr. Gopinath Sutendra

INTRODUCTION

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

METHODS

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

RESULTS

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

CONCLUSIONS

The novel interaction and differential regulation of p53-transcriptional activity and apoptosis by PKM2 could provide the basis for novel therapeutic strategies against CIC.

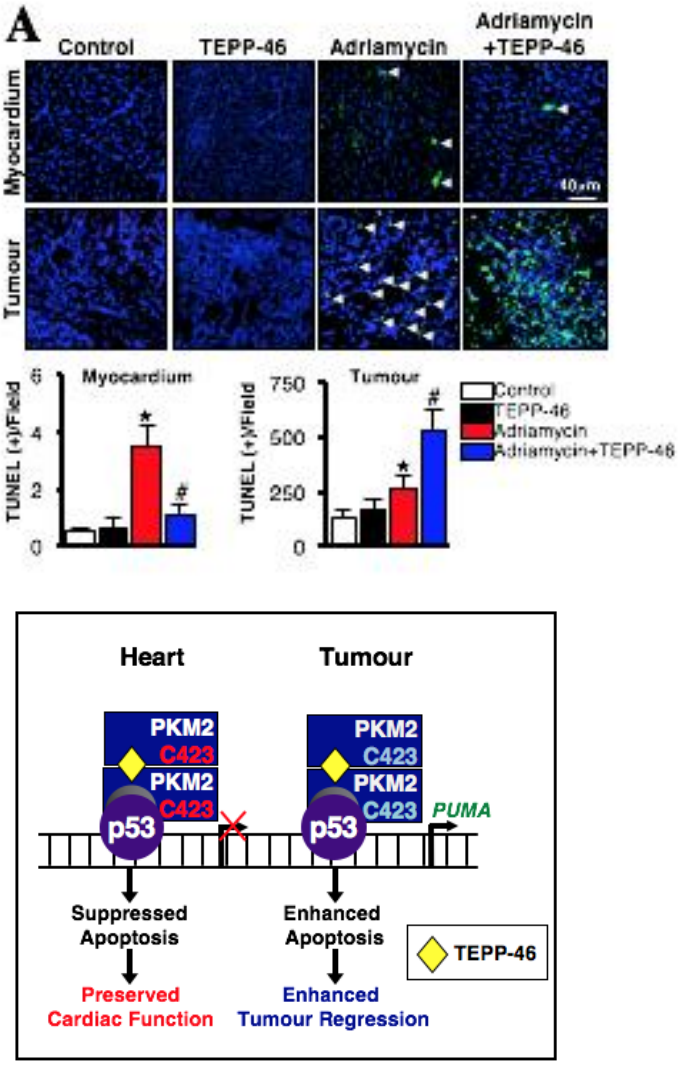

Figure: Therapeutically stabilizing PKM2 with TEPP-46 inhibits p53 transcription activity and apoptosis in the heart, while enhancing p53 activity and apoptosis in the tumor.
A. PKM2 stabilization via TEPP-46 prevents Adriamycin-mediated apoptosis in the heart (measured by TUNEL staining in green, nuclear stain DAPI in blue) while further enhancing apoptosis in the tumor of xeno-transplanted mice with human lung cancer (n=5 mice/group, * denotes $p<0.05$ vs control, # denotes $p<0.05$ vs Adriamycin).
B. Cysteine-423 of PKM2 is preferentially oxidized in the heart compared to the tumor. Stabilization of dimer PKM2 with TEPP-46 results in inhibition of p53 transcriptional activity and apoptosis in the heart preserving cardiac function while enhancing p53 transcriptional activity in the tumor enhancing tumor regression.

External validation and improvement of EHMRG risk model using a population-based cohort of patients with heart failure

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Supervisor: Dr. Justin A. Ezekowitz

INTRODUCTION
Emergency Heart Failure Mortality Risk Grade (EHMRG) is a 10-item risk score that was developed to assess the risk of dying in the next 7 days for patients with acute heart failure (AHF) in the emergency department (ED). However, it lacks key variables including natriuretic peptide (NP) values and widely used triage scores. We aimed to externally validate and refine the EHMRG risk model using a cohort of patients who presented to ED via ambulance with AHF.

METHODS
Cohort study using administrative data of all ambulance-transported patients from Alberta (2012 - 2016) presenting to the ED with a primary diagnosis of acute HF (ICD-10 I50.x). The C-index and Net reclassification improvement (NRI) were used to assess overall model quality.

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

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

Supervisor: Dr. Justin A. Ezekowitz

Table. EHMRG model performance in predicting 7-day death

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

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

Identifying low-risk patients for early discharge from emergency department without using subjective descriptions of chest pain

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

INTRODUCTION
Several accelerated diagnostic protocols (ADP) have been developed to allow emergency department (ED) physicians to identify which patients are appropriate for early discharge after presentation with chest pain. Most ADPs modify the algorithm based on the subjective chest pain characteristics. We investigated the performance of 3 established major ADPs, simplified by eliminating the need for chest pain as a descriptor.

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

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

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

Supervisor: Dr. Justin A. Ezekowitz

Table: Operating characteristics of the different rules

	sVCPR	sEDACS-ADP≥3	ADAPT-ADP
Primary outcome of ACS diagnosis within 30 days			
Sensitivity	99.1 (96.8, 99.9)	97.3 (94.2-99.0)	98.7 (96.1-99.7)
Specificity	12.0 (9.9, 14.3)	16.1 (13.7-18.7)	4.9 (3.6-6.6)
PPV	22.5 (19.9, 25.3)	23.1 (20.4-25.9)	21.1 (18.7-23.8)
NPV	98.1 (93.3, 99.7)	95.8 (91.2-98.5)	93.3 (81.7-98.6)
Secondary outcome of 30-day cardiac events			
Sensitivity	100 (97.6, 100)	100 (97.5, 100)	100 (97.6, 100)
Specificity	11.3 (9.3, 13.5)	15.4 (13.2, 17.9)	4.8 (3.5, 6.4)
PPV	15.4 (13.2, 17.8)	16.0 (13.7, 18.5)	14.5 (12.4, 16.7)
NPV	100 (96.6, 100)	100 (97.4, 100)	100 (92.1, 100)
Identified as low risk, %	9.7	13.3	4.1

ACS: Acute Coronary Syndrome; ADAPT: Accelerated Diagnostic protocol to Assess Patients with chest pain using contemporary Troponins as the only biomarker; ADP: Accelerated Diagnostic Protocol; NPV: negative predictive value; PPV: positive predictive value; sEDACS: the simplified emergency department assessment of chest pain score; sVCPR: simplified Vancouver Chest Pain Rule;

Factors influencing ambulance use in patients with suspected acute coronary syndromes: a population-based geographic information system study

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

INTRODUCTION
Despite all public awareness campaigns and guideline recommendations, the majority of patients with symptoms suggestive of acute coronary syndrome (ACS) do not use emergency medical services (EMS) to reach the emergency department (ED). The aim of this study was to investigate the factors associated with EMS utilization and subsequent patient outcomes.

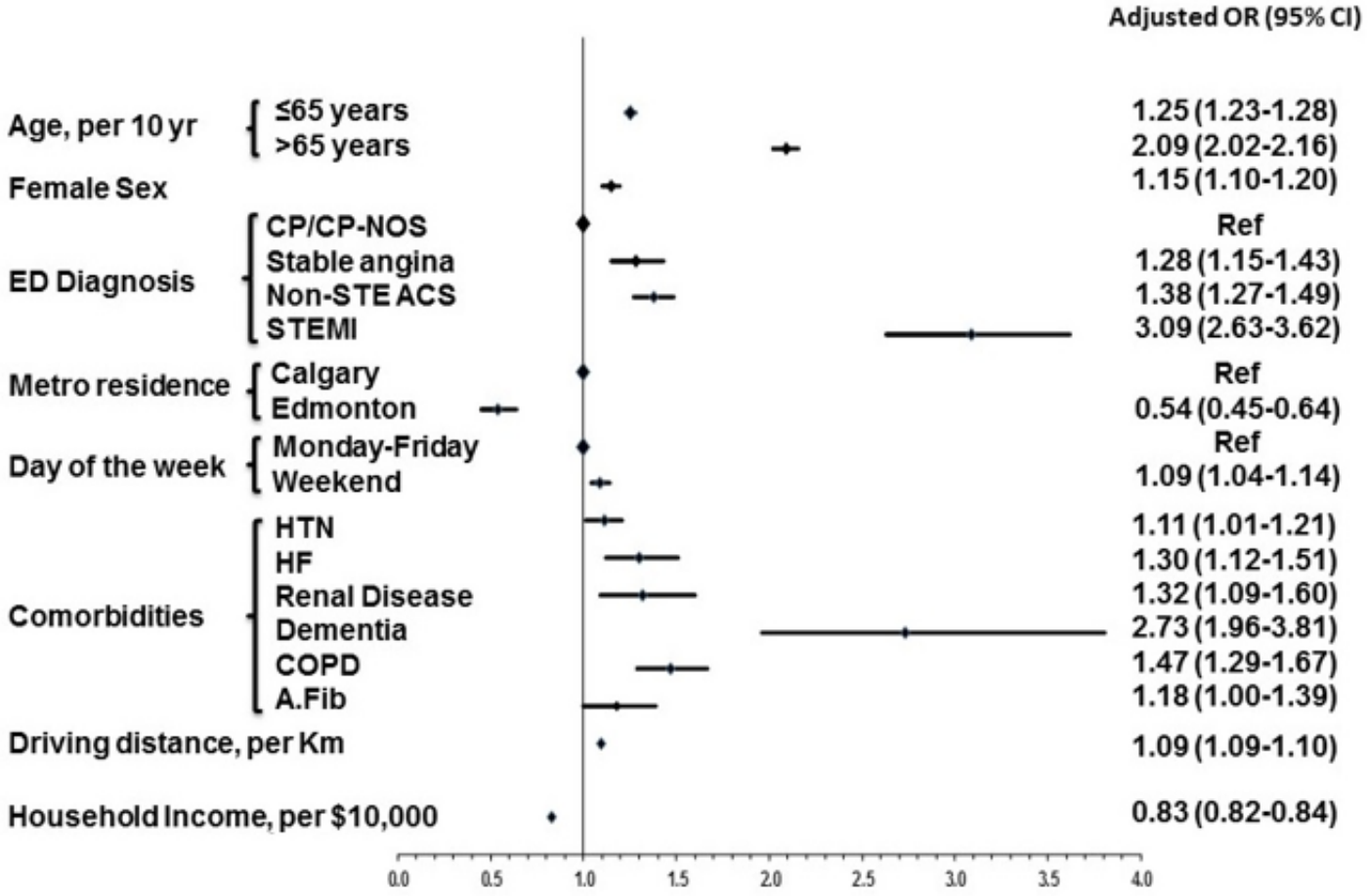
METHODS
We used data from the metropolitan areas of Edmonton and Calgary, which are of similar size and in the same public health system (population ~3 million people). Using administrative health databases, all patients who presented to an ED in the years of 2007-2013 with main ED diagnosis of ACS,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

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

CONCLUSIONS
Several demographic and clinical features were associated with higher EMS use including geographic variation. This has implications for the design of EMS systems, triage and early diagnosis and treatment options.

Supervisor: Dr. Justin A. Ezekowitz

Figure. Factors associated with the mode of ED presentation (EMS versus self-transport)



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

Use of Probiotics, Prebiotics and Dietary Fibre Supplements in Patients with Inflammatory Bowel Disease

Melissa Silva, Richa Chibbar, Jens Walter, Karen Goodman, Ammar H. Keshteli, Rosica Valcheva, Levinus A. Dieleman
Supervisor: Dr. Levinus Dieleman

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic intestinal inflammatory conditions likely induced by abnormal immune response to resident intestinal bacteria in genetically susceptible hosts. Probiotics, prebiotics and dietary fibres alter the gut microbiota and improve its function, thus potentially counteracting the development of inflammation. Although the role of these compounds in the prevention and management of IBD is relatively understudied, anecdotal evidence suggests widespread, undocumented use of these supplements by patients. Our aim is to present pilot data from a study designed to estimate the association between the intake of probiotics, prebiotics and dietary fibre supplements and disease severity in patients with IBD.

METHODS

A cross-sectional study using a 20-item survey questionnaire and retrospective chart review was used in patients with a diagnosis of IBD in the IBD Clinic at the University of Alberta. Data on demographics, disease characteristics, knowledge and use of probiotics, prebiotics and dietary fibre supplements was collected. Disease duration and medication type were tabulated as indicators of disease severity.

RESULTS

In this pilot study, 23 participants (13 males, 10 females) with a known diagnosis of IBD (57% ulcerative colitis [UC], 39% Crohn’s disease [CD], 4% indeterminate colitis) completed survey questionnaires. Sixty five percent of surveyed patients have used these products in the past (58% UC, 42% CD). The use of these alternative therapies was higher in patients with longer history of IBD (71% in those with a duration >5 years vs. 29% in those with a duration <5 years. Interestingly, 50% of patients on biologics reported past usage, suggesting use after treatment failure.

CONCLUSIONS

This pilot study shows that a large proportion of IBD patients with longer disease duration who have tried multiple treatments have used probiotics, prebiotics and dietary fibre supplements in the past, despite the lack of well-proven efficacy. Further investigation is needed to confirm these findings.

Supervisor: Dr. Levinus Dieleman

Donor body mass index (BMI) does not impact recipient BMI following fecal microbiota transplantation for recurrent Clostridium difficile infection

Smith, Justin; Roach, Brandi; Silva, Marisela; Louie, Thomas; Xu, Huiping; Kao, Dina
Supervisor: Dr. Dina Kao

INTRODUCTION

Fecal microbiota transplantation (FMT) is effective for recurrent Clostridium difficile infection (RCDI). Although guidelines exist for stool donor screening, there is no recommendation on donor BMI. A case of new-onset obesity was reported in a patient receiving FMT from an overweight donor. However, it remains unknown whether donor BMI has any significant impact on recipient BMI.

METHODS

Seventy-two patients with RCDI were part of an RCT receiving FMT by colonoscopy or by capsules. The donors had BMIs dichotomized into normal BMI (18.3, 20, and 21 kg/m squared) and high BMI (24.9, 25.4, and 30 kg/m squared). Weight/height were measured pre-FMT, 1 week, 4 weeks and 12 weeks post-FMT. Weight lost during RCDI was recorded. Participant characteristics were compared using the two-sample t-test and Pearson chi-square test. Changes in BMI were assessed using the paired-t test and the repeated measures mixed effects model examined how BMI changed over time and effect of donor/method of delivery.

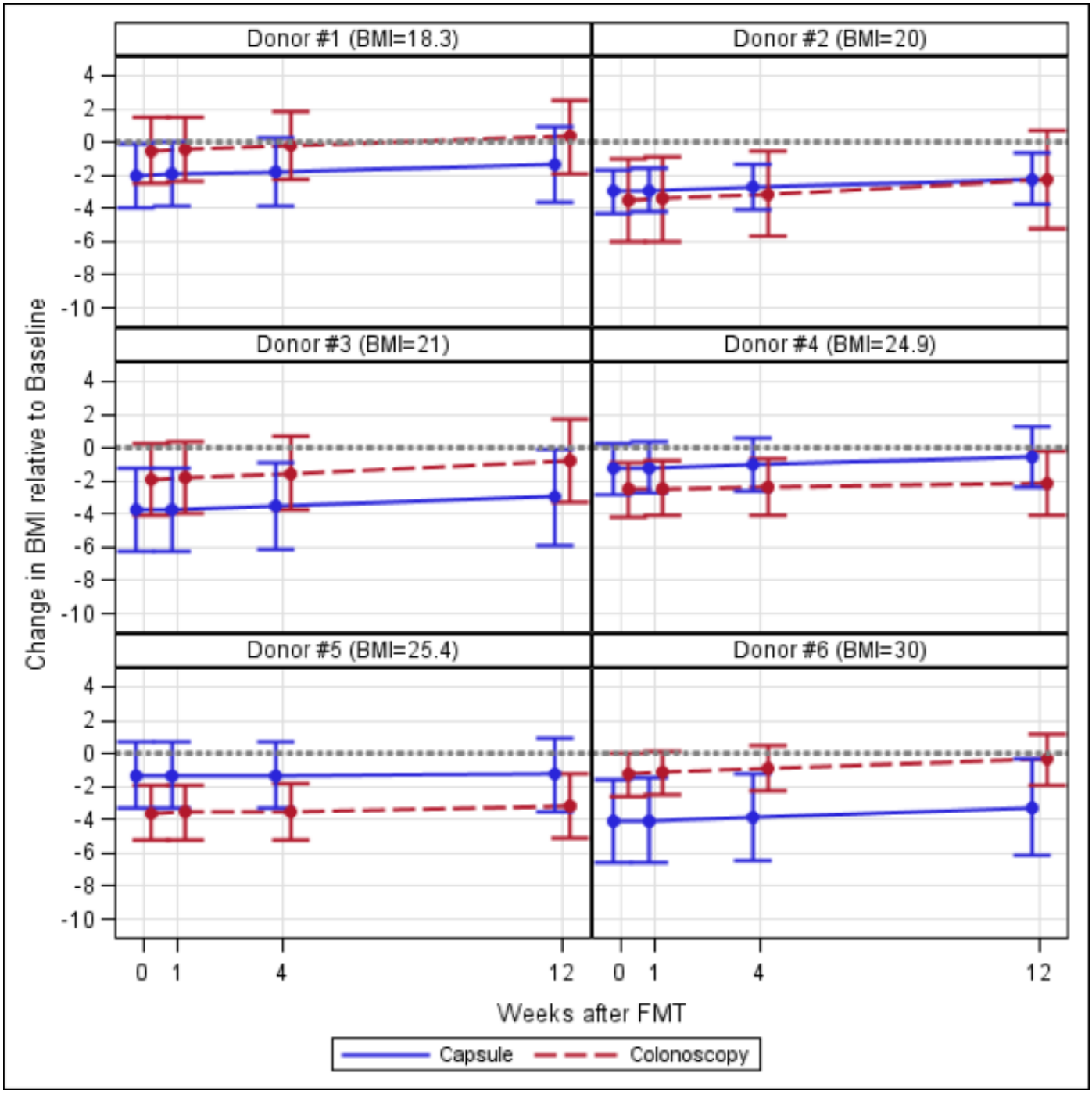
RESULTS

There were no significant differences in baseline characteristics between patients receiving stool from a normal-BMI vs high-BMI donor. The mean reported weight loss from RCDI was 6.2 ± 6.1 kg, corresponding to a mean BMI 2.3 ± 2.2 lower than baseline before developing RCDI ($p<0.001$). The BMI improved by an average of 0.73 ± 1 relative to pre-FMT BMI; however, this was still significantly lower than baseline ($p<0.001$). Twenty-five patients (35%) had gained weight above their baseline, while the remaining 47 patients (65%) had not regained their lost weight. Participant BMI improved 0.71 (95% CI: 0.46 – 0.96; $p<0.001$), independent of stool donors ($p=0.41$) and method of delivery ($p=0.55$).

CONCLUSIONS

Although there was improvement over time, 65% of patients did not return to their weight at baseline despite successful FMT during 12 weeks of follow-up. The change in weight was not related to donor BMI or delivery method.

Supervisor: Dr. Dina Kao


Donor #1 (BMI=18.3)
Donor #2 (BMI=20)
Donor #3 (BMI=21)
Donor #4 (BMI=24.9)
Donor #5 (BMI=25.4)
Donor #6 (BMI=30)
Change in BMI relative to Baseline
4
2
0
-2
-4
-6
-8
-10
0
1
4
12
Weeks after FMT
Capsule
Colonoscopy

U18666A-induced Cholesterol Sequestration Differentially Regulates APP Metabolism in Normal and APP Overexpressing Cells

J. Y. Chung, M. Stahn, A. Mohamed, M. Maulik, G. Thinakaran, E.I. Posse de Chaves 3 and S. Kar
Supervisor: Dr. Satyabrata Kar

INTRODUCTION

Amyloid β (Aβ) peptide derived from amyloid precursor protein (APP) plays a critical role in the development of Alzheimer's disease (AD). Current evidence indicates that cholesterol level/subcellular distribution can regulate Aβ production and clearance, but it remains unclear how accumulation of cholesterol within the endosomal-lysosomal (EL) system, the major site of Aβ production, can influence APP metabolism.

METHODS

In the present study, we evaluated the effects of U18666A, a class II amphiphile which triggers intracellular redistribution of cholesterol within EL system, on mouse N2a cells expressing different levels of APP in the presence or absence of extracellular cholesterol/lipids provided by fetal bovine serum (FBS).

RESULTS

Our results revealed that U18666A and FBS differentially increased levels of APP and its cleaved products α- and β-C-terminal fragments (CTFs) in mouse N2a cells expressing normal levels of mouse APP (N2awt) or higher levels of human wildtype APP (APPwt) or the "Swedish" mutant APP (APPsw). Our results also revealed that U18666A significantly enhanced η-CTF levels in all three cells types, but only when cells were cultured with high FBS concentrations. Additionally, cellular levels of Aβ1-40 were markedly increased in U18666A-treated APPwt and APPsw cells, while secretory levels of Aβ1-40 decreased in all three cell lines. U18666A treatment was found to trigger an increase of APP at the cell surface at all FBS conditions. Our results further revealed that APP and its cleaved products following cholesterol sequestration are partly accumulated in the lysosomes possibly due to decreased clearance. Finally, we show that serum delipidation attenuated the levels of APP-CTFs, but not APP holoprotein, observed following U18666A treatment at high FBS concentrations.

CONCLUSIONS

Collectively, these results suggest that cholesterol sequestration within EL system, depending on the levels and nature of APP express in the cells, can differentially regulate APP metabolism which can subsequently influence the development of AD-related pathology.

Supervisor: Dr. Satyabrata Kar

Development of a histologically validated segmentation protocol for the hippocampal body

Trevor A Steve, MD FRCPC1 ; Clarissa L Yasuda, MD PhD2 ; Roland Coras, MD3 ; Mohjevan Lail1; Ingmar Blumcke, MD3 Daniel J Livy, PhD4 ; Nikolai Malykhin, MD PhD5 Donald W Gross, MD FRCPC1
Supervisor: Dr. Donald W Gross

INTRODUCTION

In the present study, we aimed to: 1) develop a novel histology-based method for hippocampal body segmentation and assess its accuracy in comparison to the gold standard direct histological measurements; 2) quantify the accuracy of three published segmentation strategies in comparison to the histological gold standard; and 3) apply the novel method to ex vivo MRI and correlate the results with histology.

METHODS

Ultra-high resolution ex vivo MRI was performed on six whole cadaveric hippocampal specimens, which were then divided into 22 blocks and histologically processed. A novel method was developed using mean percentage of the total stratum lacunosum moleculare (SLM) distance to define subfield boundaries. Boundary distances and subfield areas on histology were then determined using the novel method and compared to the gold standard histological measurements. The novel method was then used to determine ex vivo MRI measures of subfield boundaries and areas, which were compared to histological measurements.

RESULTS

For direct histological measurements, the mean percentages of total SLM distance were: Subiculum/CA1 = 9.7%, CA1/CA2 = 78.4%, CA2/CA3 = 97.5%. Ex vivo MRI measurements using the novel method were strongly correlated with direct measurements of SLM length, CA1/CA2 boundary, and CA2/CA3 boundary, but not for Subiculum/CA1 boundary. Subfield areas measured with the novel method on histology and ex vivo MRI correlated with gold standard histological measures for CA1, CA2, and CA3/CA4/dentate gyrus (DG).

CONCLUSIONS

In this initial proof of concept study, we used ex vivo MRI and histology of cadaveric hippocampi to develop a novel segmentation protocol for the hippocampal body. The novel method provided accurate measurements of CA1, CA2, and CA3/CA4/DG subfields in comparison to the gold standard histological measurements. The correlation demonstrated between histology and ex vivo MRI supports the potential feasibility of applying this method to in vivo MRI studies.

Supervisor: Dr. Donald W Gross

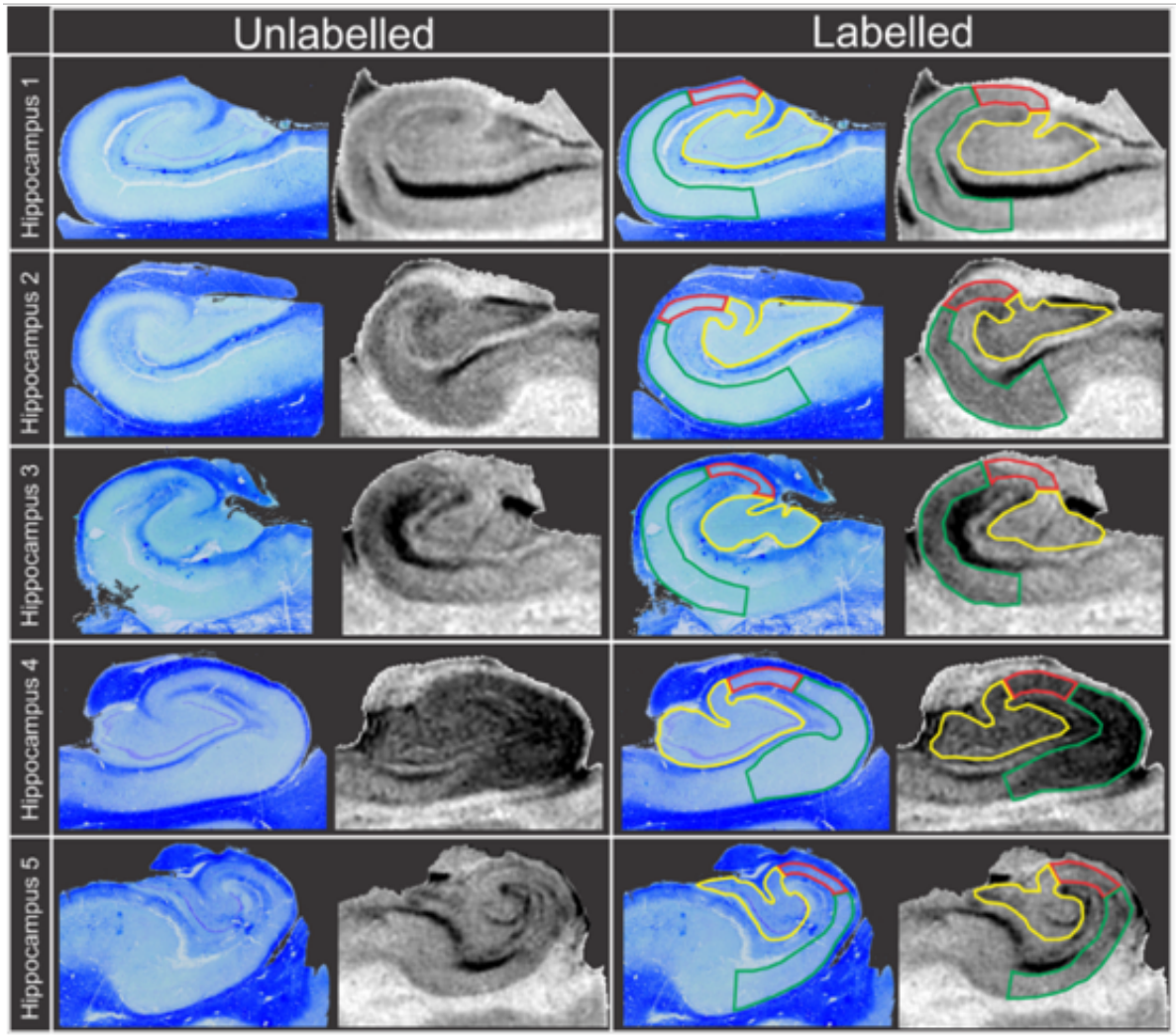


Figure - Subfield area measurements:

Corresponding histology and ex vivo MRI slices are displayed for five separate hippocampi, allowing qualitative analysis of coregistration success (unlabelled panel). In all corresponding sections (Labelled, total n=19), the novel method was applied to segment separate areas for three subfields: CA1 (green), CA2 (red), and CA3/CA4/DG (yellow)

Would Cross-Jurisdictional Collaboration of Provincial Tuberculosis Programs be Beneficial? An analysis of Tuberculosis Transmission in the Canadian-Born across the Prairies between 2006 and 2010

Varughese, M.(1,2), Heffernan, C.(3), Sharma, M.(4), Li, Michael (1), and Long, R.(2,3)
Supervisor: Dr. Michael Li and Dr. Richard Long

INTRODUCTION

Canada, is a large country comprised of a few high density and many sparsely populated areas. Although healthcare services in Canada are designed to be equitable among all Canadians, geographical and jurisdictional challenges associated with delivery can create barriers to access. For example, tuberculosis (TB) cases are not equally distributed among all population groups or community types. Some Indigenous communities experience a much greater burden of TB. The use of surveillance data can help assess jurisdictional challenges that impact communicable diseases such as TB, which is not bound by provincial or community borders.

This study aims to use surveillance data for TB collected in connection with a seven-year study called the “Determinants of TB Transmission (DTT)” project to assess whether provincial TB programs across the prairies are appropriately managing TB transmission among the Canadian-born population.

METHODS

Surveillance data from the DTT project included quantitative questionnaires and molecular epidemiological data. Quantitative questionnaires included demographic, risk factor, and mobility information among Canadian-born culture positive pulmonary TB cases across the prairies between 2007 and 2008. Genotyping analysis using 24-loci (Mycobacterial interspersed repetitive units) fingerprints was conducted among all TB isolates between 2006 and 2010. Clustering was defined as TB isolates that had an identical fingerprinting pattern.

RESULTS

Ninety percent (223/248) of culture positive pulmonary TB cases in Canadian-born adults in the prairies were diagnosed among Indigenous peoples. Evidence of clustering and mobility patterns identified the potential for TB transmission to extend beyond provincial and community borders. Clustering across provinces occurred in 47% of TB cases in the Indigenous population. Issues relating to healthcare access on-reserve may be an additional factor for increased transmission due to the travel associated with accessing healthcare services off-reserve.

CONCLUSIONS

Cross-jurisdictional collaboration of provincial TB programs and increased surveillance would be beneficial in helping to reduce potential TB transmission

across the prairies.

Supervisor: Dr. Michael Li and Dr. Richard Long

RIGHT VENTRICULAR FUNCTION AND REMODELING PREDICT OUTCOME IN PATIENTS WITH HEART FAILURE PHENOTYPES

Lingyu Xu1,2, Harris Wang1, Kelvin Chow2, Joseph J. Pagano2, Anna R. Schmidt5, James White5, Mark J. Haykowsky3, Evangelos D. Michelakis1, Justin A. Ezekowitz1, Jason R. Dyck4, Gavin Y. Oudit1, Richard B. Thompson2, D. Ian Paterson1
Supervisor: Dr. Ian Paterson

INTRODUCTION

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

METHODS

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

RESULTS

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

CONCLUSIONS

RV abnormalities are prevalent among patients with HFREF and HFPEF phenotypes. RVE have additional prognostic value over conventional LV parameters. Routine assessment of RV on CMR is recommended in all cases of possible HF.

Supervisor: Dr. Ian Paterson

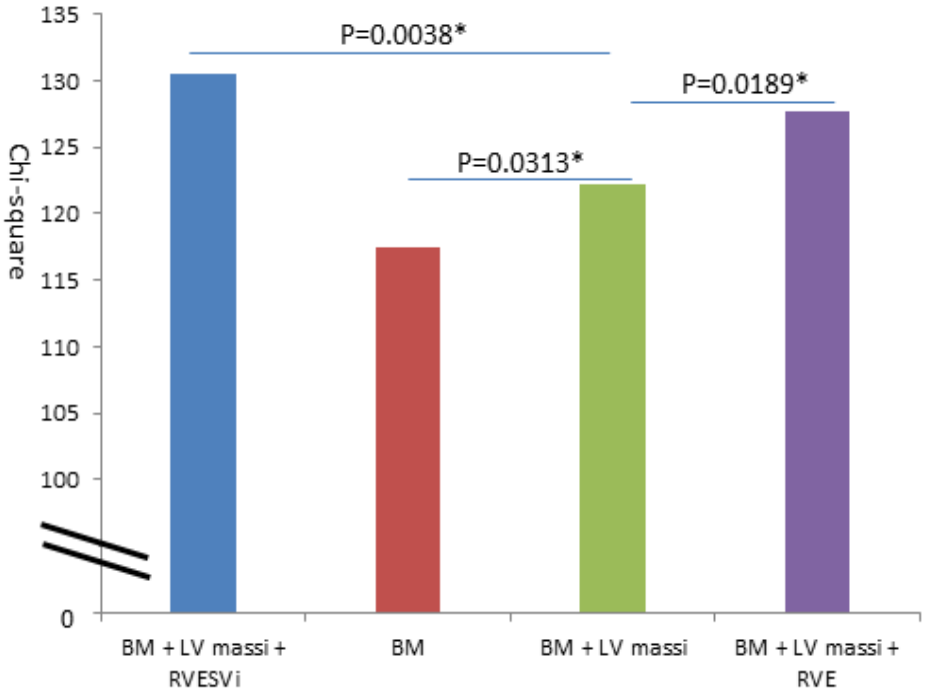


Figure 2. Additive Prognostic Value of CMR Measures in Heart Failure Cohort
Incremental χ^2 score by stepwise inclusion of indexed LV mass, RVE or RVESVi in addition basic model in Cox proportional hazard regression models among patients overall.

A comparative analysis of computational approaches for the identification and quantification of urinary metabolites in 1H NMR spectra

Marc Cassiède1, Pascal Mercier2, Paul Shipley3, Meghan Dueck1, Sindhu Nair1, James Mino1, Samineh Kamravaei1, Lindsey Felix1, Bernadette Quémerais1, and Paige Lacy1
Supervisor: Dr. Paige Lacy

INTRODUCTION

Proton nuclear magnetic resonance (1H NMR) spectroscopy is widely used for the identification and quantification of urinary metabolites. However, intense clusters of peaks and spectral overlap in most regions of NMR spectra make it challenging to accurately analyse individual metabolites. As it is important to select suitable candidate metabolites to allow statistical analysis, we show that appropriate criteria may be utilized to filter urinary metabolites using pooled quality control (QC) samples. In this work, we present a new method of metabolite peak detection and measurement based on the deconvolution of complex experimental NMR spectra with a target reference signal.

METHODS

Using pooled replicate QC samples (31) from our welding study, we carried out NMR analysis and obtained averaged spectra from 10 measurements of each QC sample using a 600 MHz magnet equipped with a robot sample handler at the NANUC NMR Centre. We then applied spectra deconvolution of 151 known urinary metabolites to QC samples. We assessed the percentage relative standard deviation (%RSD) obtained from median values of 10 repeated fits on each sample. We then compared these with %RSD values obtained from a novel computer-based algorithm (Monte Carlo (MC) simulation), and compared this with the existing peak-fitting method using Chenomx NMR Suite.

RESULTS

Using our first peak analysis based on %RSD < 20%, we determined that 62 metabolites could be reproducibly measured in the QC samples. Following a separate MC simulation on the same samples, the number of metabolites that “passed” this test was reduced to 60 and a total of 43 metabolites were shared between the two methods.

CONCLUSIONS

Our study demonstrates that correct interpretation of urinary NMR spectra is difficult to achieve with computer-based algorithms. Our MC simulation analysis is still under development and is expected to generate improved peak detection and measurement in urine samples.

Supervisor: Dr. Paige Lacy

Perturbations in Brain Peroxisome Function and Biogenesis in Multiple Sclerosis

Manmeet K Mamik 1, Leina Saito 2, William Branton 1, Richard Rachubinski 3 and Christopher Power 1
Supervisor: Dr. Christopher Power

INTRODUCTION

Peroxisomes are eukaryotic subcellular organelles with multiple functions including catalase-mediated detoxification of reactive oxygen species (e.g. hydrogen peroxide), β-oxidation and catabolism of very-long chain fatty acids, and biosynthesis of plasmalogens that are essential for myelination. Multiple sclerosis (MS) is a progressive inflammatory demyelinating disease, principally affecting white matter in the central nervous system (CNS). Myelinating oligodendrocytes are the chief target cell in MS. We have begun to investigate peroxisome biogenesis and function in relation to MS pathogenesis.

METHODS

RNA and protein were prepared from the CNS white matter (CNS-WM) of MS (n=6) and other disease control (ODC; n=6) age- and sex-matched patients. Massively parallel RNA sequencing (RNA-Seq) was performed, and sequences were identified by alignment with established human transcriptome databases. Peroxisome and inflammatory transcript levels were investigated by RT-PCR in cultured human progenitor-derived oligodendrocytes (PDO) with/without TNF-α exposure and in MS and ODC CNS-WM. Peroxisome-associated protein immunoreactivity was assessed by western blot and immunocytochemistry of CNS-WM from MS and ODC patients.

RESULTS

RNA-Seq analyses revealed increased abundance of transcripts associated with peroxisome biogenesis (PEX1, PEX5, PEX10) in MS CNS-WM samples, accompanied by increased inflammatory gene expression. PDOs showed reduced peroxisomal enzyme gene (e.g. catalase, HSD17B4) expression ($p<0.05$) following TNF-α exposure. PEX7 and PEX13 transcript levels were upregulated together with inflammatory genes in MS compared to ODC, but in contrast catalase, thiolase and aspartoacylase transcript levels were reduced in MS compared to ODC CNS-WM ($p<0.05$). Both western blot and immunohistochemical analyses showed reduced catalase immunoreactivity in MS CNS-WM ($p<0.05$).

CONCLUSIONS

These findings show dichotomous changes in peroxisome gene expression in MS, defined by induction of some biogenesis genes with concurrent reduced enzymatic genes in both CNS-WM and cultured oligodendrocytes, highlighting potential perturbations in peroxisome function in MS.

Supervisor: Dr. Christopher Power

Development of a Performance Assessment Tool for the Computer-Assisted Rehabilitation Environment

Juan Forero, Jeremy Hall, Albert Vette, Jacqueline Hebert
Supervisor: Dr. Jacqueline Hebert

INTRODUCTION

An important aspect in rehabilitation is the accurate assessment of the impairment. This is usually performed through the use of clinical measures aimed at depicting different characteristics of balance and mobility. However, those measures are 1) limited to the specific population for which they were designed; and 2) typically most sensitive to those with moderately severe deficits. The Computer Assessed Rehabilitation Environment (CAREN) is ideal for assessing balance and mobility in a wide range of individuals (e.g., neurological injury, musculoskeletal injury, high performance populations). We aim at developing a Performance Assessment Tool for the CAREN to provide objective balance and mobility assessments for patients.

METHODS

A series of tasks were designed based on the main components of currently available outcome measures for balance and performance. The content validity for the proposed tasks and scoring systems was assessed by surveying clinicians and content experts, and refined based on input and feedback to minimize ceiling effects. Kinematics, kinetics, and response time data will be collected continuously while the participant performs the tasks.
The reliability and construct validity of the proposed task scores will be determined in 50 able-bodied individuals and 25 with balance and mobility impairments due to lower limb amputation or traumatic brain injury. Each participant will be tested on the full task battery and also on standard functional mobility outcome tests to appraise validity. Able-bodied participants will be tested twice on the full task battery by two different raters to assess test-retest / inter-rater reliability.

RESULTS

The proposed assessment tasks have been programmed on the CAREN. Recruitment and data collection will begin in April once the programs final adjustments based on pilot experiments have been completed.

CONCLUSIONS

This tool will help clinicians identify specific deficits to be targeted with treatment, and allow measurement of improvement over time.

Supervisor: Dr. Jacqueline Hebert


10:41:53
99
Hills 1.0 3.5 kph
Incline -0.2 1.0 m/s
Lateral -0.3 2.2 mph
Hits: 16 of 18

The impact of body mass index in cirrhotic patients with septic shock: a retrospective cohort study

Beverley Kok, Juan G Abraldes, Rajiv Jalan, Anand Kumar, Constantine J Karvellas
Supervisor: Dr. Constantine Karvellas

INTRODUCTION
There is equipoise regarding obesity and outcomes in critically ill patients with sepsis/septic shock. The relationship between critically ill septic patients with cirrhosis and mortality has not been defined.

METHODS
A nested cohort study of all cirrhotic patients with septic shock (n=379) and a recorded body mass index (BMI) from an international, multicentre (CATTS) database (1996-2015) was performed. Patients were classified as overweight (BMI 25-30), obese (BMI 30-40) or morbidly obese (BMI > 40) as per WHO categories. Logistic regression was used to determine independent associations with in-hospital mortality.

RESULTS
In this analysis, the mean age was 56.1 (SD 12.3) years and 62% were male. Median BMI was 26.3 (22.7-32.0). 58.1% were overweight or obese. In-hospital mortality was 70%. Compared to non-obese patients (n=159), overweight/obese patients (n=220) were more likely to have comorbidities of cardiac, lung disease or diabetes (p value < 0.001 for all). Comparing hospital survivors (n=111) vs non-survivors (n=268), survivors demonstrated lower MELD (30.5 vs. 10.1), APACHE II scores (22.4 vs. 29.1) and number of organ failures (4.3 vs. 5.4) ($p < 0.001$ for all comparisons). Survivors had lower rates of nosocomial infection (30.6% vs 52.6 %, $p < 0.001$) and lower requirements for renal replacement therapy (9% vs. 47%, $p = 0.019$) or mechanical ventilation (66.7% vs. 92.4%, $p < 0.001$).

Using multivariable logistic regression to adjust for confounding, delay in administration of appropriate antimicrobial therapy (OR 1.14 per hour, $p < 0.001$), APACHE II (OR 1.10, $p < 0.001$), peak lactate (OR 1.15, $p = 0.005$) and BMI (OR 1.06 per increment increase, $p = 0.018$) were independently associated with in-hospital mortality. This model performed well (c-statistic 0.874).

CONCLUSIONS
In cirrhotic patients with septic shock, increasing BMI is independently associated with increased mortality after adjusting for covariates reflecting severity of illness.

Supervisor: Dr. Constantine Karvellas

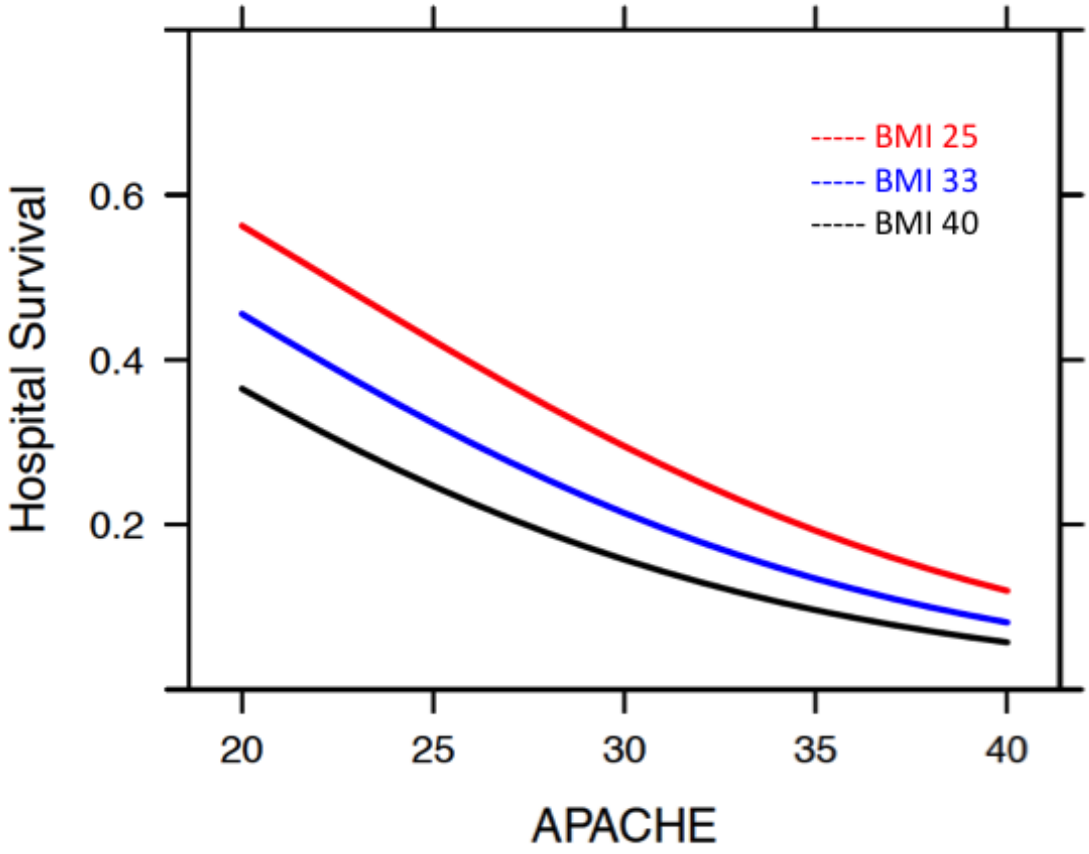


Figure 1. Relationship between decreasing hospital survival according to increasing BMI is synergistic with increasing APACHE scores. Regression lines for BMI of 25, 33 and 40 have been selected as representative.

Personalizing Obesity Assessment and Care Planning in Primary Care: Patient Experience and Self-management Outcomes

THEA LUIG, ROBIN ANDERSON, ARYA M SHARMA, DENISE L CAMPBELL-SCHERER
Supervisor: Dr. Denise Campbell-Scherer

INTRODUCTION

This study explores patient experiences of personalized obesity management consultations in primary care and their impact on patients' everyday efforts to improve health.

Root causes for obesity include comorbid diseases and psychosocial factors. Despite available resources, patients' needs for strategies to navigate their personal barriers to obesity management are currently not sufficiently met. There is a pressing need for effective interventions that guide clinicians in personalizing assessment and care planning to improve patient health.

We developed an intervention integrating the 5As of obesity management with the collaborative deliberation model for care communication. This presentation focuses on how patients experience the intervention and make changes to improve health as a result.

METHODS

Purposeful sampling of 20 patients. Video-recorded consultations, semi-structured patient interviews, patient diaries and two follow-up interviews to document self-management over several months. Inductive, thematic analysis in NVIVO11.

RESULTS

Three themes emerged as central to achieving a personalized intervention from the patient perspective: (1) the clinician anchored the assessment in the patient's story; (2) the story helped identify preferences and strategies to address root causes and barriers that then informed the care plan; and (3) co-telling their story with the clinician helped patients shift toward increased awareness of connections between their life events, emotions, behaviours, and health; increased self-efficacy; positive self-image; and realistic expectations for weight management. These are interpersonal processes that underpinned pertinent intervention elements, such as patient story, shared decision-making, and motivational interviewing, and that were decisive for patients to make changes to improve health.

CONCLUSIONS

Preliminary findings suggest that interpersonal processes occurring during collaborative, personalized obesity consultations are key in supporting patient self-efficacy and self-management as well as for coordinating interdisciplinary clinical care to improve health outcomes. Results will refine the intervention and identify patient outcome measures in preparation for a future trial.

Supervisor: Dr. Denise Campbell-Scherer

Evaluating Who Benefits from Research: Community Engagement and Enhancing Capacity Throughout the Research Process

Megan J. Highet, Amy Colquhoun, Megan Lukasewich, Karen J. Goodman, the Fort McPherson H. pylori Project Planning Committee, and the CANHelp Working Group
Supervisor: Dr. Karen Goodman

INTRODUCTION

We present a photovoice project developed in partnership with the Fort McPherson H. pylori Project planning committee, comprised of community residents, designed to meet the dual priorities of research that addresses community concerns regarding H. pylori infection in Fort McPherson, NT, and research activities that provide learning opportunities for youth by involving them in research.

METHODS

This community-driven project was developed through the collaborative efforts of University of Alberta researchers, community leaders, and the students and principal of Fort McPherson's Chief Julius School. This participatory project aimed to explore community perspectives surrounding the impact of H. pylori infection, while the research design itself sought to provide participants with training and education in scientific research methods throughout the project.

RESULTS

An important goal of this project was to elucidate the research processes that take place once academic researchers leave the community. We aimed to achieve this by continuing to engage youth in the process of research analysis and dissemination through a project-sponsored visit to our offices at the University of Alberta. Here, we describe the photovoice project conducted with students at Chief Julius School and outline the activities that took place during the youths' week-long visit to Edmonton.

CONCLUSIONS

We conclude with a discussion of the merits of this approach drawn from the perspectives of academic researchers, community members, and the youth research partners.

Supervisor: Dr. Karen Goodman

Towards characterizing the significance of astrocytic Aβ in AD pathogenesis

Olaide Oyegbami, Serene Wohlgemuth, Victor Foroutanpay, Sang-Gyun Kang, Jing Yang, David Westaway, and Satyabrata Kar.
Supervisor: Dr Satyabrata Kar

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a gradual loss of memory. Mutation of the Amyloid Precursor Protein (APP) gene is associated with a subset of early-onset familial AD. The neuropathological features associated with AD include the presence of intracellular neurofibrillary tangles, extracellular plaques and loss of selected neurons in the brain. Neurofibrillary tangles contain mainly hyperphosphorylated tau proteins while plaques include a compact deposit of beta-amyloid (Aβ) peptides surrounded by activated astrocytes.

Astrocytes are the most abundant glial cells in the CNS. They play vital roles in regulating neurotransmitter release, synapse formation and maintaining brain homeostasis. In response to injury or development of neurodegenerative diseases such as AD, astrocytes undergo activation, characterized by hypertrophy of cellular processes and upregulation of intermediate filament proteins including glial fibrillary acidic protein (GFAP). They also express pro-inflammatory molecules that can induce an inflammatory reaction, possibly contributing to the loss of neurons and the development of AD pathology.

METHODS

Some studies indicate that targeting activated astrocytes may serve as a therapeutic tool in the treatment of AD. However, there is no mouse model available to evaluate how APP/Aβ overexpression in astrocytes can influence AD pathology. To address this issue, we have recently developed a line of transgenic mouse expressing human APP in astrocytes (GFAP-APP751 Tg mice) and evaluated how Lipopolysaccharide (LPS; 2.5mg/kg)-mediated inflammatory response can influence AD-related pathology in GFAP-APP751 Tg and control littermates.

RESULTS

GFAP-APP751 Tg mice exhibit increased levels of APP in astrocytes along with alterations in some proteins (ADAM10 and Nicastrin) associated with APP endoproteolysis. LPS treatment causes early and short-lasting peripheral and CNS inflammatory responses along with an increased level of APP holoprotein in astrocytes.

CONCLUSIONS

We are currently evaluating how increased levels of astrocytic APP can influence Aβ production and AD-related pathology in GFAP-APP751 Tg mice.

Supervisor: Dr Satyabrata Kar

Effect of fecal microbial transplantation on microbial and phage composition in patients with recurrent Clostridium difficile infection

Park, HeeKuk; Millan, Braden; Hotte, Naomi; Kao, Dina H; Madsen, Karen
Supervisor: Madsen, Karen

INTRODUCTION

The gut microbiome contains a diverse bacteriophage community that plays a largely unknown role in shaping microbial colonization and disease pathogenesis. Fecal microbial transplantation (FMT) is the most effective therapy for recurrent Clostridium difficile infection (RCDI) and has been shown to transfer phages along with gut microbes. Aim this study was to examine the effects of FMT on microbial and phage composition in RCDI patients.

METHODS

Patients with RCDI (n=19) received FMT from donors via colonoscopy. Stool samples were collected prior to and following FMT. DNA was extracted and sequenced for metagenomic analysis for bacteria and phage composition. To understand of growth dynamics of E. coli were inferred from the metagenomic data with mapped genome coverage.

RESULTS

In RCDI patients prior to FMT, Proteobacteria dominated. RCDI patients also harbored numerous phages within the Myoviridae and Siphoviridae family. In contrast, the gut microbiome of donors consisted primarily of Bacteroides and Firmicutes; donors also had a much reduced phage population. Eleven patients were successfully treated with a single FMT (FMT-S) while 8 patients required multiple FMTs (FMT-M). A successful FMT resulted in the appearance of donor phages in the RCDI recipients with a complete loss or significant reduction of phages and increased Bacteroidetes and Firmicutes. This was associated with an increased inferred growth rate of Escherichia coli suggesting that E. coli and associated phages may be driving disease pathogenesis in some RCDI patients that fail to respond to FMT.

CONCLUSIONS

RCDI patients had decreased microbial diversity but increased numbers and diversity of phages compared with healthy individuals. A successful FMT altered both bacterial and phage composition to resemble the donor. Patients who required at least two FMT had significant differences in their phage population suggesting that the presence of particular phages may have a role in modulating response of patients to fecal transplantation.

Supervisor: Dr. Madsen, Karen

Characterization and propagation of the Human Betaretrovirus: a potential etiological agent in primary biliary cirrhosis

Weiwei Wang, Stanislav Indik, Shawn T. Wasilenko, Gane Ka-Shu Wong , Steven Willows, Andrew Mason
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease that leads to cholangitis and destruction of interlobular bile ducts. Our lab has previously characterized a retrovirus in patients with PBC called human betaretrovirus (HBRV) due to its similarity to the betaretrovirus mouse mammary tumor virus (MMTV). Despite several papers from our lab supporting this etiology, existence of this virus is controversial as, like MMTV, it is suspected that only very low levels of virus is present in patients. To provide further evidence for its existence and to provide a source of virus for further experimentation, our lab sought to isolate and propagate HBRV in a tissue culture model.

METHODS

We co-cultured Hs578T cells, a human breast cancer cell line, with homogenized lymph nodes from PBC patients, and single cells were isolated by limiting dilution. Infection status was probed by assaying for reverse transcriptase activity (RT) activity and through qRT-PCR of the pol and env genes. Supernatants from infected cells were both subjected to electron microscopy analysis and used to infect biliary epithelial cells (BEC) via coculture, with infection status being monitored by in situ hybridization. To further prove that virus was actually infecting Hs578T cells, we assessed the sites of integration of HBRV in the Hs578T genome using ligation-mediated PCR.

RESULTS

Hs578T cells that were positive for reverse transcriptase activity and by qRT-PCR were found to release virus-like particles with acentric cores consistent with previous studies on betaretrovirus morphology. Coculture studies showed HBRV RNA in previously uninfected BEC cells 8 and 12 days post-infection. We also found 611 unique integration sites in Hs578T cells, which were mostly distributed randomly throughout the genome.

CONCLUSIONS

Our current data provides further evidence for the existence of HBRV and prove that virus can be passaged in tissue culture.

Supervisor: Dr. Andrew Mason

The Role of Laboratory Tests in Monitoring Systemic Lupus Erythematosus: A Systematic Review

Alforaih N (1), Touma Z (2), Chatterley T (1), Keeling SO (1)
Supervisor: Dr. Stephanie Keeling

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, often characterized by periods of flare and remission. Multiple laboratory studies are used by clinicians to aid in monitoring SLE patients. While some disease activity and damage instruments include certain laboratory tests as part of their descriptors, further evaluation is needed to identify which laboratory tests are useful in predicting disease outcome. This systematic literature review was performed to identify which laboratory tests were associated with lupus outcomes including flare and damage.

METHODS

MEDLINE, EMBASE, and the Cochrane Library databases were searched up to April 2016 for literature highlighting the PICO: population = SLE, intervention(s) = laboratory tests (eg. CBC, C3, C4, ds-DNA, creatinine), comparison = self, outcome(s) = flare, disease activity, damage, mortality. The quality of evidence was assessed by the Newcastle Ottawa scale.

RESULTS

Our literature search yielded 12548 articles, out of which 305 articles were identified following title and abstracts screen. A total of 53 articles met the inclusion criteria. Twenty-seven studies (47%) demonstrated that anti-ds-DNA antibodies was predominately a marker of disease activity, and to a lesser extent, damage or morbidity. Twenty-six studies (43%) highlighted that low complements (C3 or C4) were associated with disease activity, specifically as a marker of renal involvement. C-reactive protein was associated with disease activity in 7 studies (13%). Cytopenias appeared to be associated with disease activity/flare in 6 studies (9%) for anemia, 5 studies (7%) for thrombocytopenia, and 7 studies (11%) for leukopenia. Renal indices associated with disease activity included urinalysis, 24hr urine protein and spot urine protein:creatinine ratio in 8 studies (15%).

CONCLUSIONS

The biomarkers anti-ds-DNA antibodies and complements correlated with the worsening disease activity and damage as evidenced by studies in this systematic review. In comparison, other lab parameters provided less clear evidence of their role in monitoring the lupus patient.

Supervisor: Dr. Stephanie Keeling

ffect of Advanced Age, Elevated Bilirubin, and Disease Extent on Outcomes of Unresectable Pancreatic Cancer (UPC) Patients Receiving First-line Chemotherapy: A Population-Based Study.

M. Ho (1), Y. Wang (3), H. Cherniawsky (2), S. Ghosh (1), W. Cheung (3)
Supervisor: Maria Ho

INTRODUCTION

Superiority of FOLFIRINOX (FFN) and nab-paclitaxel plus gemcitabine (NG) over standard gemcitabine (GEM) monotherapy for UPC was shown in the PRODIGE and MPACT trials respectively. However, both trials either excluded or limited enrollment of patients with locally advanced disease, elevated bilirubin and advanced age. We sought to determine the impact of age, bilirubin and disease extent on treatment outcomes in the real-world setting.

METHODS

We identified all patients newly diagnosed with UPC who received palliative chemotherapy at the Cross Cancer Institute in Alberta or any 1 of 6 British Columbia Cancer Centres between January 2014 to April 2016. Receipt of at least one cycle of chemotherapy represented treatment with group assignment based on the initial regimen delivered. Outcomes were compared and adjusted for age, bilirubin, extent of disease, and other measured confounders.

RESULTS

292 patients were identified with 161 (55%) were age 65 or older, 74 (25%) had elevated bilirubin, and 205 (70%) had metastatic disease at the time of presentation. Patients who received FFN or NG had a longer median overall survival than those treated with GEM alone after adjusting for age, ECOG, bilirubin and extent of disease (11 vs 10 vs 4 months, respectively; FFN: HR 0.297, 95% CI 0.199-0.445, $p < 0.0001$, and NG: HR 0.338, 95% CI 0.236 – 0.485, $p < 0.0001$). Similarly, FFN and NG patients also had longer progression-free survival in comparison to GEM alone (8.8 vs 6.9 vs 2.9 months, respectively; FFN: HR 0.33, 95% CI 0.22-0.499, $p < 0.0001$, and NG: HR 0.47, 95% CI 0.33 – 0.67, $p < 0.0001$). Advanced age and elevated bilirubin were not significantly associated with either outcome ($p > 0.05$).

CONCLUSIONS

The efficacy of FFN and NG were superior when compared to GEM alone for patients with UPC suggesting that the benefits of FFN and NG persisted regardless of advanced age and hyperbilirubinemia.

Supervisor: Dr. Maria Ho

The Impact of Advanced Care Planning in Idiopathic Pulmonary Fibrosis

Dr. Meena Kalluri, Dr. Alia Daoud
Supervisor: Dr. Meena Kalluri

INTRODUCTION

The implementation of advanced care planning in the KEC Multidisciplinary (MD) ILD Clinic lead to increased adherence to patient preferred location for care and death, increased utilization of palliative approach and decrease health resource utilization at end of life defined as last 6 months prior to death when compared to published literature in Interstitial Pulmonary Fibrosis.

METHODS

-Retrospective Descriptive Study.
-Identification of all IPF/ILD deaths that occurred in ILD clinic population since inception of clinic 20012-current)and their electronic medical records will be reviewed.
-Extraction of all relevant data as described below to build a profile of the symptom burden faced by patients and the palliative care they received including medical and non- medical therapies, provision of allied health consults, home care assessments and health care utilization in the year preceding their death (ER visits, hospitalization, doctor visits). We will collect information to ensure that the IPF diagnosis is accurate (review HRCT and lung biopsy results to confirm diagnosis). This is important to ensure other types of ILD are excluded. Disease severity in IPF is measured by assessment of lung function (pulmonary function tests- PFTs, 6 minute walk tests-6 MWT). This data will be collected from clinic charts. It is important to correlate disease severity with services required in order to plan for an effective intervention.
-Use of descriptive statistics such as mean, median with standard deviation.

RESULTS

In progress.

CONCLUSIONS

In progress.

Supervisor: Dr. Meena Kalluri

Role of EBV status and use of immunosuppressants in patients with IBD who subsequently develop lymphoma

Grace Lam, Lindsy Ambrosio, Anthea Peters, Brendan Halloran, and Richard Fedorak
Supervisor: Dr. Brendan Halloran

INTRODUCTION

Immunosuppressive agents, such as thiopurines and biologics, have revolutionized the treatment of inflammatory bowel disease (IBD). However, a number of studies have identified a concerning link between immunosuppression and lymphoproliferative disorders (LPDs). These LPDs have been associated with Epstein-Barr virus (EBV) infection. Here, we conduct a retrospective study to determine the LPD incidence in our local IBD population and a prospective study to examine if adoption of an EBV serologic surveillance protocol can minimize LPD risk in the IBD population.

METHODS

The retrospective study was conducted by keyword search of the Zeidler Ledcor IBD Center's electronic medical records from 2014-2016 using the qualifiers "IBD" and "lymphoma" and by manual chart review of the Alberta Cancer Registry from 2014-2016 to identify those with IBD. Identified charts were reviewed for age, gender, IBD status, type of immunosuppressants used, type of lymphoma and year of IBD and lymphoma diagnoses. In the prospective study, IBD patients older than 18 years of age were recruited for an initial test of baseline EBV serology and monitored over time with regards to their EBV status and viral load as they initiate IBD treatment.

RESULTS

We identified 12 IBD patients who developed lymphoma after initiation of treatment out of the 8,607 unique IBD patients in the Edmonton Zone. 3 were EBV associated LPD. Imuran was prescribed in all 3 cases. In the prospective arm, 121 patients have been recruited to date. None have been diagnosed with LPD since the start of the study one year ago.

CONCLUSIONS

Our data indicates that LPD occurs locally at an incidence rate of 0.14% similar to the rates reported elsewhere in the world. As 21% of LPD were EBV associated, we await the results of the prospective study to determine if EBV monitoring in IBD patients on immunosuppressants can reduce the risk of LPD development.

Supervisor: Dr. Brendan Halloran

Immunoglobulin replacement therapy in patients with COPD and Hypogammaglobinemia; a retrospective study

Dr. Shwan Mohydeen(1) Dr. Eric Wong(2) , Dr. Bruce Ritchie(3) and , Dr. Harissios Vliagoftis (2)
Supervisor: Harissios Vliagoftis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in Canada. Mildly decreased IgG levels are common in patients with severe COPD and frequent infections and can be attributed to smoking, the use of corticosteroids, or older age. However, there is a lack of data regarding the utility of screening for hypogammaglobulinemia in patients with COPD and the efficacy of IgG replacement for those with low IgG levels.

METHODS

We conducted a retrospective chart review of all the patients with pulmonary function test confirmed COPD, treated with IgG replacement at the primary immune deficiency clinic of the University of Alberta. Emergency room visits for COPD exacerbation for the two years before and 2 years after the initiation of IgG replacement was the primary outcome. Secondary outcomes included numbers of hospitalization, antibiotic prescriptions, pulse steroids prescriptions, rescue bronchodilator prescriptions, anticholinergic inhaler prescriptions and spirometry values.

RESULTS

431 patients were reviewed and 9 patients fulfilled the criteria for COPD diagnosis and were followed for at least two years after initiation of treatment. Two of them had normal IgG levels and were on IgG replacement for IgG subclass deficiency and the other 7 had low IgG ranging from 5.05-6.71 g/L before initiation of IgG replacement. The number of emergency room visits trended towards decreasing after IgG replacement ($p=0.089$). There was a significant decrease in the requirement for antibiotics ($p=0.042$), but no changes in the other secondary outcomes.

CONCLUSIONS

IgG replacement might be beneficial for patients with COPD and low IgG levels as these subjects showed a trend for decreased emergency room visits and significantly decreased antibiotic use. A larger cohort prospective study is warranted to address those outcomes in order to develop algorithms for IgG replacement for patients with COPD and low IgG.

Supervisor: Dr. Harissios Vliagoftis

Table 1.1 Study outcomes by before and after treatment (n=9)

	Before Median (IQR)	After Median (IQR)	P value
ER visits	2 (0 – 3)	0 (0 – 1)	0.089
Hospital admissions	1 (0 – 1)	0 (0 – 1)	0.341
Pulse steroid prescriptions	2 (0 – 4)	1 (0 – 2)	0.345
Antibiotics prescription	7 (5 – 8)	2 (1 – 3)	0.042
Bronchodilators prescriptions	4 (3 – 6)	3 (1 – 4)	0.105
Inhaled steroids prescriptions	2 (1 – 4)	1 (1 – 2)	0.242
Inhaled anticholinergic prescriptions	2 (1 – 3)	1 (1 – 2)	0.720
FEV1 L/Sec	1.48 (1.00 – 1.79)	1.33 (1.09 – 1.65)	0.734
FEV1% predicted	68 (54 – 73)	65 (56.5 – 71.0)	0.859
IgG level	6.13 (5.76 – 7.23)	10.18 (8.62 – 12.5)	0.059

“DOCS”: Donor Offer Call Simulation; a novel tool to evaluate nephrology and kidney transplant trainees in managing deceased donor kidney offers

Monika Oliver BSc MD, Kevin Wen MD, Hatem Alnasser MD, Allan Murray MD, Sita Gourishankar MD MSc
Supervisor: Oliver

INTRODUCTION

Competence in accepting deceased donor kidney (DDK) offers for transplantation is a curricular expectation of nephrology/transplant trainees. Yet the current curriculum dedicates minimal formalized training to the refinement of this skill. We assessed trainees’ competence in accepting DDK offers by reviewing their performance following participation in a Donor Offer Call Simulation (DOCS) exercise.

METHODS

A standardized DOCS rubric was developed for the purposes of assessing participants’ preparedness in accepting DDK calls. Seven categories, known to be relevant to decision making for organ allocation, graft outcome and acceptance or discard of an organ, were examined. One nephrology and two transplant trainees participated in two DOCS, typical of DDK offer. Two silent observers witnessed the simulations and scored participants using the DOCS rubric, with points awarded for probing and successfully acquiring key donor information.

RESULTS

All three participants reported increased confidence and competence in participating in donor offer calls following completion of the DOCS. Mean scores for both simulation scenarios were 54.14% (Range 35.02%-7.9%, $p<0.05$).

Performance was correlated with level of training; with the two transplant fellows consistently outperforming the nephrology trainee ($p<0.5$). Notably the transplant trainees at the end of the training year still missed between 25-50% of critical information.

CONCLUSIONS

DOCS identified important competency gaps in trainees for accepting DDK offer calls. This highlights the need for improved training practices implemented early in the nephrology-training curriculum. DOCS is a highly efficient and cost effective model that can be easily incorporated into current training practices. A potential exists to implement the DOCS scoring rubric into clinical practice to systemize the donor offer process thus ensuring complete information acquisition and enhance reproducibility between calls.

Supervisor: Dr. Oliver

"DOCS": Donor Offer Call Simulation

A novel tool to evaluate nephrology and kidney transplant trainees in managing deceased donor kidney offers

Monika Oliver BSc, Kevin Wen MD, Hatem Alnasser MD, Allan Murray MD, Sita Gourishankar MD MSc

UNIVERSITY OF CALGARY

BACKGROUND

•In Northern Alberta, the Human Organ Procurement and Exchange Program (HOPE) is responsible for the deceased organ donation process.

•When a donor becomes available, the HOPE Coordinator places a "donor offer" call to the organ specific transplant team, who are responsible for reviewing the quality and suitability of the organ for transplantation.

•Competence in assessing suitability and adequacy of deceased donor kidneys for transplantation is a curricular expectation of nephrology and transplant trainees.

RESEARCH OBJECTIVES

1.To assess trainees' competence in accepting deceased donor kidney (DDK) offers by reviewing their performance following participation in a Donor Offer Call Simulation (DOCS) exercise.

2. To identify areas of weakness in trainee's knowledge of important donor assessment criteria.

3. To improve the preparedness of trainees receiving DDK offers and limit acceptance/rejection of organs based on inadequate donor history.

METHODS

•A standardized DOCS rubric was developed for the purposes of assessing trainees preparedness in accepting DDK calls.

• Seven categories, known to be relevant to decision making for organ allocation, graft outcome and acceptance or discard of an organ were examined.

• One nephrology (R5) and two transplant trainees (R7a, R7b) participated in two DOCS, typical of a DDK offer. In each DOCS, the HOPE coordinator placed a call to the participant and revealed donor history when probed.

•Two silent observers witnessed the simulations and scored participants using the DOCS rubric, with points awarded for probing and successfully acquiring key donor information.

RESULTS

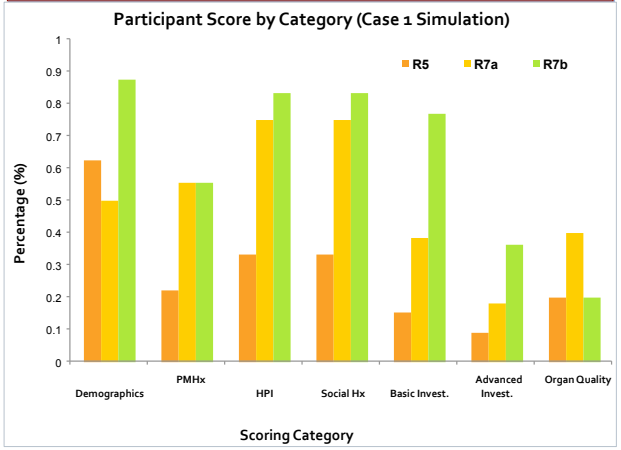


Table 1

Comparison of trainee scores by rubric category. Scores are reported as percentages. Displayed data is for the Case 1 simulation only. Scores are based on the average of points awarded by each investigator.

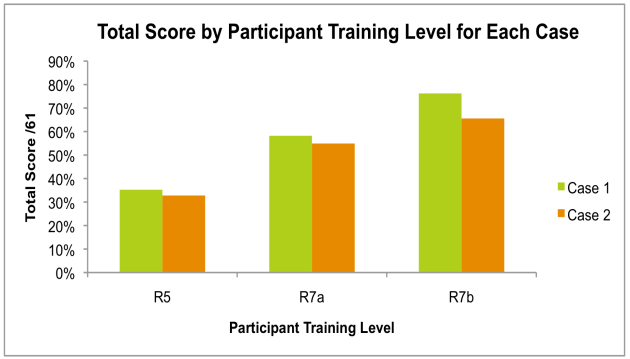


Table 2

Comparison of total score for each simulation scenario by participant training level. Scores are based on the average of total scores awarded by each investigator. It should be noted that case 2 was developed to be more difficult than case 1. Mean scores for both simulation scenarios were 54.14% (Range 35.02%-70.9%, p<0.05).

SUMMARY

•DOCS identified important gaps in trainee preparedness for accepting DDK offers. Namely, participants consistently scored poorly in the "advanced investigations" and "organ quality' categories".

•Performance was correlated with level of training; with the two transplant fellows consistently outperforming the nephrology trainee ($p<0.5$). Notably the transplant trainees at the end of the training year still missed between 25-50% of critical information. Of note, the staff reference comparison score was 97%.

•Participants reported increased confidence and preparedness when accepting DDK offers following DOCS training, highlighting the need for improved training practices implemented early in the training curriculum.

CONCLUSIONS

• DOCS is a highly efficient and cost effective model that can be easily implemented into current training practices to improve trainee confidence and competence accepting DDK offers.

• A potential exists to implement the DOCS scoring rubric into clinical practice as a standardized intake form to streamline the donor offer intake process and allow for increased reproducibility between calls to ensure complete donor information acquisition.

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ACKNOWLEDGEMENTS

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Exploring the role of sex hormones in driving symptom severity in ME/CFS

Lindsey Russell 1, Gordon Broderick 1,2, Jeanna M Harvey 3,4, Zachary M Barnes3,5, Fanny Collado3, Elizabeth Balbin4, Nancy G Klimas2,3, Mary Ann Fletcher2
Supervisor: Dr. Gordon Broderick

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex multi-factorial illness that involves immune and endocrine dysfunction. Our objective was to explore the role of sex hormones on symptom exacerbation.

METHODS

Illness severity was characterized using standard self-assessment instruments incuding Multidimensional Fatigue Inventory (MFI). Blood samples were collected at rest from n=38 female ME/CFS subjects, 18-63 years of age, and analyzed for concentrations of testosterone, estradiol and progesterone. Subjects were divided into four groups, based on age (50 years) and progesterone levels with the luteal phase as progesterone > 1.1 ng/ml and follicular phase as < 1.1 ng/ml. Concentrations were log2 transformed and z-scaled. Standard T-tests were used to compare to hormone concentrations and ratios across groups, adjusted for false discovery using Benjamini Hochberg criteria. Spearman correlation was used to link progesterone and hormone ratios to general and physical fatigue within groups.

RESULTS

Despite comparable MFI severity scores sub-groups differed significantly testosterone (avg. 15.4 ng/dL, SE 2.9), estradiol (avg 100ng/ml, SE 36), and progesterone (avg 3.58 ng/ml, SE 0.69) levels suggesting changes in illness mechanisms. In women age <50 yrs, testosterone correlated negatively with general fatigue at progesterone <1.1ng/mL ($p=0.01$) subgroup. Conversely at high progesterone status testosterone correlated positively with fatigue ($r=0.68$, $p=0.01$). For age < 50 years, progesterone correlated negatively with general fatigue at low progesterone status ($r = 0.43$, $p=0.03$). In older women (≥ 50 yrs), estradiol correlated positively with general fatigue at higher progesterone status ($r = 0.61$, $p=0.03$).

CONCLUSIONS

These result indicate that sex hormones, particularly testosterone, significantly and directly associate with fatigue severity in ME/CFS subjects when controlling for menstrual phase and menopausal status. Shifting association of hormones with severity across groups suggests nonlinear, context-specific relationship. Additional analysis on measured cytokines collected and their joint effects with sex hormones on symptoms is ongoing.

Supervisor: Dr. Gordon Broderick

Exploring the role of sex hormones in driving symptom severity in ME/CFS

Lindsey Russell 1, Gordon Broderick 1,2, Jeanna M Harvey 3,4, Zachary M Barnes3,5, Armando Mendez5, Fanny Collado3, Elizabeth Balbin4, Nancy G Klimas[2,3], Mary Ann Fletcher[2,3].

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BACKGROUND

- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and poorly understood illness.
- Affects up to 4 million individuals, costing $35 billion dollars in lost productivity and healthcare in the US alone.
- Disproportionately high in women.
- Studies of regulatory physiology supports endocrine-immune predisposition to ME/CFS in women.

Our objective was to explore the role of sex hormones on symptom exacerbation in women with ME/CFS.

METHODS

- **N=38** female ME/CFS subjects, 18-63 years of age.
- Illness severity characterized using standard Multidimensional Fatigue Inventory (MFI).
- Blood collected at rest analyzed for estradiol, testosterone and progesterone levels.
- 4 subject groups, based on age (< 50 yrs, ≥ 50 yrs), luteal phase progesterone >1.1 pg/ml and follicular phase as <1.1 pg/ml.
- Concentrations log2 transformed and z-scaled. Standard T-tests applied to hormone concentrations and ratios across groups.
- Partial Spearman correlation ***corrected for BMI*** linking progesterone, testosterone and hormone ratios to general and physical fatigue within groups with $r > 0.40$.
- Adjusted for false discovery using Benjamini Hochberg criteria FDR<0.05.

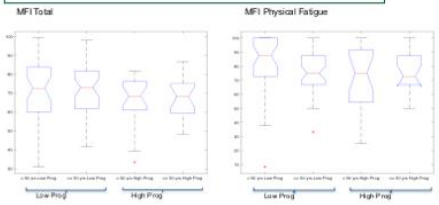

Figure 1.0. Total and physical fatigue scores are similar between both age groups and progesterone status.

RESULTS

- Despite comparable MFI severity scores sub-groups differed significantly testosterone (avg. 15.4 ng/ dL, SE 2.9), estradiol (avg 100pg/ml, SE 36), and progesterone (avg 3.58 ng/ml, SE 0.69) levels suggesting changes in illness mechanisms.
- Progesterone differed significantly different between age groups when >1.1ng/ml (p=0.028).
- Changes in estrogen approached significance between age groups (p=0.057) at low progesterone.
- In women age < 50 yrs, ***testosterone*** correlated ***negatively*** with general fatigue at progesterone <1.1ng/mL (r = -0.49, p=0.01) subgroup(Figure 2.0).
- Conversely at high progesterone status ***testosterone*** correlated ***positively*** with fatigue (r=0.68, p=0.01) (Figure2.0).
- For age < 50 years, ***progesterone*** correlated ***negatively*** with general fatigue at low progesterone status (r = 0.43, p=0.03), but did not reach significance at higher ranges.
- In older women (≥ 50 yrs), **estradiol** correlated ***positively*** with general fatigue at higher progesterone status (r = 0.61, p=0.03) (Figure 3.0).
- No significant correlations were found at lower progesterone .
- Correlation improved using E:P ratio for both general (r = 0.90, p<0.01) and physical fatigue (r = 0.84, p<0.01) (Figure 3.0).

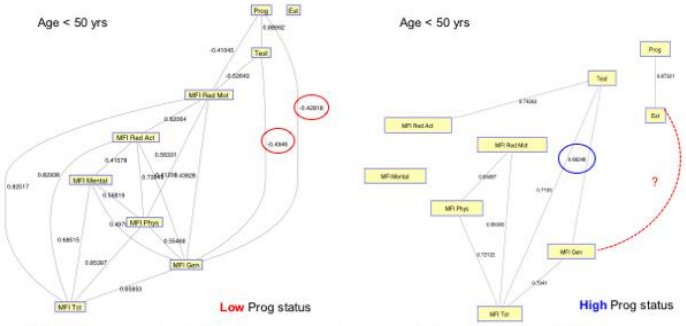

Figure 2.0. In the lower prog cohort, both testosterone and progesterone negatively correlated to General Fatigue (red circles). In women with high prog status, testosterone positively correlated with fatigue (blue circle) and progesterone had no relation (red line).

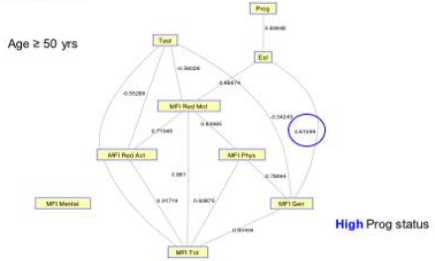

Figure 3.0. In the older cohort, estradiol positively correlated to General Fatigue, p=0.03.

CONCLUSION

- Sex hormones, particularly ***testosterone***, significantly and directly associate with fatigue severity in ME/CFS.
- **Shifting association of hormones with severity across groups suggests *nonlinear, context-specific relationship*.**
- Strengths include broad contextual survey of immune and endocrine function across a range of symptom severity.
- Limited sample frequency does not support the inference of regulatory causal associations.
- Analysis incorporating cytokine expression and their joint effects with sex hormones on symptoms is ongoing.
- Androgen receptors are also emerge in ongoing genomic studies being conducted on ME/CFS cohorts.

ACKNOWLEDGEMENTS

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The authors declare that they have no competing interests.

Mononeuritis Multiplex Possibly Related to IgG-4 Case Report and Review of the Literature

Leanna Tsang & Elaine Yacyshyn
Supervisor: Dr. Elaine Yacyshyn

INTRODUCTION

IgG4-related diseases (IgG4-RD) are uncommon but can affect the pancreas, salivary gland, and lacrimal glands, with increasing cases affecting other tissues being described. Features of IgG4-RD include: subacute painless swelling, dense tissue infiltration of IgG4 plasma cells and small lymphocytes, storiform fibrosis, obliterative phlebitis, tissue eosinophilia, elevated serum IgG4 levels, and responsiveness to glucocorticoid therapy.

METHODS

.

RESULTS

A previously healthy 47-year old male presented with mononeuritis multiplex initially with unilateral peroneal neuropathy, and rapidly progressed to include bilateral ulnar neuropathies. Imaging and laboratory investigations were unremarkable, including negative ANCA, ANA, RF, ENA, cryglobulin screen, and normal CRP, SPEP, ACE level, and free kappa lambda chain assay. Infectious work-up including Hepatitis B and C, syphilis, HIV, and Lyme disease were negative. His electromyography demonstrated severe ulnar nerve axonal damage with complete atrophy of the abductor digiti minimi muscle, and a persistent peroneal nerve palsy. Sural nerve biopsy revealed non-specific inflammatory infiltration (lymphoid predominant) with the presence of eosoinophils.

He subsequently developed recurrent episodes of pancreatitis. Computerized tomography scan of the pancreas was modestly enhanced, and concerns for primary autoimmune pancreatitis could not be ruled out.

Given his rapid progression of neuropathy, he received intravenous immunoglobulins, glucocorticoids and cyclophosphamide, then transitioned to methotrexate maintenance therapy. His peripheral neuropathy stabilized with no further episodes of pancreatitis. Serum IgG-4 level was elevated at 1.00g/L while on methotrexate, which raised suspicion for IgG-4 RD. However, his sural nerve could not be re-stained for IgG-4 levels and a repeat biopsy was not indicated.

CONCLUSIONS

Our patient presented with possible IgG4-RD as the etiology for his mononeuritis multiplex and recurrent pancreatitis. To date, there is two comparable cases of IgG-4 related mononeuritis multiplex reported in the literature (Ohyama et al. (2013), Suzuki et al (2016)). Therefore, as IgG4-RD gain recognition, it should be included in the investigation of mononeuritis multiplex.

Supervisor: Dr. Elaine Yacyshyn

The Effect of Back and Feet Support on Oscillometric Blood Pressure Measurements

Jennifer S. RINGROSE, Jonathan WONG, Farahnaz YOUSEFI, Raj PADWAL
Supervisor: Dr. Raj Padwal

INTRODUCTION

Recommendations to support the back and feet during BP measurement are not always followed in clinical practice. Our objective was to determine to what extent ensuring back and feet support affects mean oscillometric blood pressure levels.

METHODS

Eighty-five consecutive, consenting participants ≥18y with BP readings between 80-220/50-120 mmHg and arm circumferences of 25-43 cm were recruited. Participants had their BP measured using an Omron HEM 907 oscillometric device. Back and feet support were examined independently. First, while the feet were supported, two sets of three BP readings were taken in random order, one with the back supported and one with the back unsupported. Next, with the back supported, two sets of three BP readings were taken in random order, one with the feet dangling and one with feet supported.

RESULTS

Mean age was 52.0±20.7y, mean arm circumference was 31.0±3.2 cm, 62% were female and 49% had hypertension. Mean BP levels with the back unsupported were slightly higher than with the back supported (119.8±15.5/69.9±8.9 vs. 119.2±16.4/68.2±8.8 mmHg; difference of 0.7±4.9/-1.8±3.0; p-value=0.21 for systolic and <0.0001 for diastolic comparisons). Mean BP levels with the feet dangling were slightly lower than with the feet supported (120.3±16.3/72.6±8.9 vs. 121.2±16.1/72.9±8.6 mmHg; difference of -0.9±4.1/-0.3±2.8; p-value=0.04 for systolic and <0.36 for diastolic comparisons). Systolic BP differences were ≥5 mmHg in 34% (back phase) and 23% (feet phase) of participants.

CONCLUSIONS

Provision of back and feet support has a small effect on mean oscillometric BP. The magnitude of effect is greatest on diastolic BP, when the back is unsupported.

Supervisor: Dr. Raj Padwal

The impact of delayed source control and antimicrobial therapy in 196 patients with cholecystitis-associated septic shock

Victor Dong, Juan Abraldes, Anand Kumar, Constantine J. Karvellas
Supervisor: Dr. Constantine J. Karvellas

INTRODUCTION

Cholecystitis-associated septic shock carries significant mortality. Treatment includes early administration of antimicrobial therapy along with source control (cholecystectomy or percutaneous cholecystostomy drainage). There is uncertainty regarding most appropriate time to achieve source control. Our aim is to determine whether timing of source control affects survival in cholecystitis patients with septic shock.

METHODS

Nested retrospective cohort study of all cholecystitis-associated septic shock patients (met Tokyo guidelines for cholecystitis along with hypotension requiring vasopressors) from an international, multicenter database between 1996 and 2015. Multivariate logistic regression analysis was performed to assess the association between practice related factors (delay to source control and antibiotics) and severity of illness on in-hospital mortality. Classification and regression tree (CART) analysis was used to evaluate the interaction between non-linear covariates.

RESULTS

Among 196 patients (mean age 69 years, 70% male), overall mortality was 37%. Compared to non-survivors (n=72), survivors (n=124) had lower mean admission Acute Physiology and Chronic Health Evaluation (APACHE) II scores (21 vs. 27, $p<0.001$) and lower median admission serum lactate (2.4 vs. 6.8 µmol/L, $p<0.001$). Survivors were more likely to receive appropriate antimicrobial therapy earlier (median 2.8 vs. 6.1 hours from shock, $p=0.012$). Survivors were also more likely to undergo successful source control earlier (median 9.8 vs. 24.7 hours, $p<0.001$). Adjusting for covariates, APACHEII [Odds ratio (OR) 1.13 (95% CI 1.06-1.21) per increment] and delayed source control >16 hours [OR 4.45 (1.88-10.70)] were independently associated with increased mortality ($p<0.001$ for all; c-statistic 0.800). CART analysis demonstrated patients with APACHEII of 15 to 26 benefited most from source control within 16 hours ($p<0.0001$; see Figure 1).

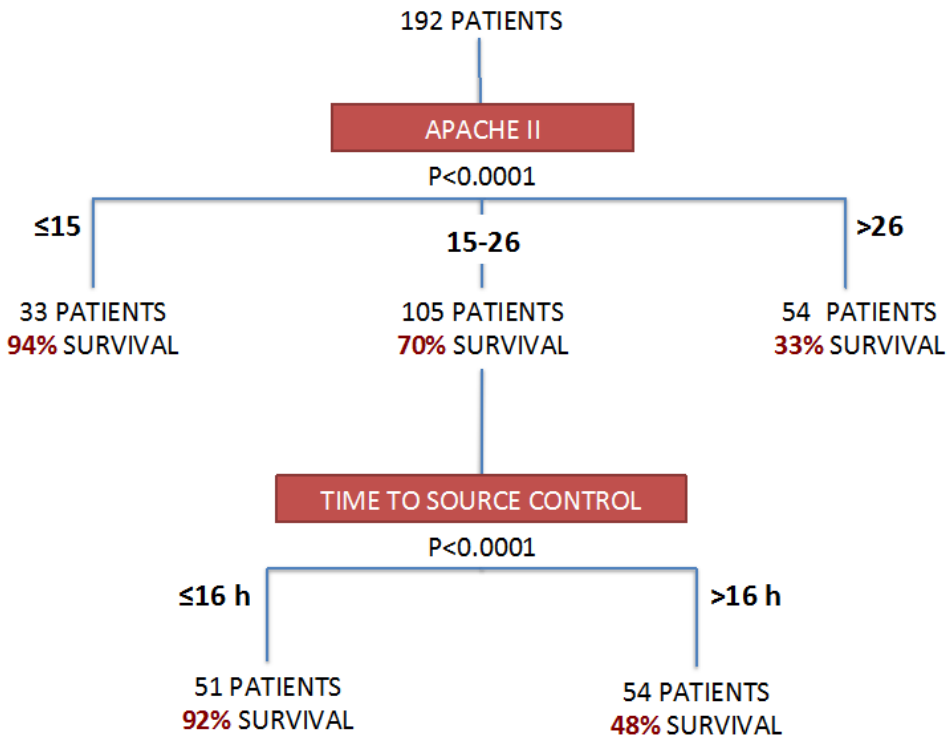
CONCLUSIONS

Patients with cholecystitis-associated septic shock have significant mortality. Admission APACHEII score and delay in source control >16 hours significantly affected hospital outcomes. This suggests urgent source control (within 16 hours) could improve outcomes in high-risk patients.

Supervisor: Dr. Constantine J. Karvellas

FIGURE 1

Classification and regression tree (CART) analysis of 192 with acute cholecystitis and septic shock.



Novel MYC Immunohistochemistry Classifier to Prognosticate in Diffuse Large B-cell Lymphoma

Cheryl Foster, Parisa Asghari-Voloshkolae, Iyare Izevbaye, Gilbert Bigras, Anthea Peters
Supervisor: Dr. Anthea Peters

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin's lymphoma and for majority of patients is curable. Progress in understanding the biology of poor prognosis DLBCL has identified that rearrangements of the MYC protooncogene confer poor response to standard chemotherapy. In addition, concurrent rearrangement of BCL2 and/or BCL6 termed "double-hit" or "triple-hit" lymphoma portends poor prognosis. MYC immunohistochemistry (IHC) has been explored as a surrogate measure of MYC gene rearrangement. However, a standardized way of quantifying MYC expression has been lacking. A new method of classifying MYC IHC has been developed to help expedite acquiring the prognostic information gained by MYC gene status. Protein overexpression that occurs without classical MYC translocation may also have relevance.

METHODS

Computerized image analysis and quantification based on distance between positive nuclei and relative stain intensity were used to classify MYC protein expression. The aim of this study was to explore whether this novel MYC IHC classifier correlates with clinical outcome for DLBCL patients. Of the 116 lymphoma samples selected to develop the classifier, there were 66 patients with DLBCL for whom clinical data was available. A retrospective chart review was undertaken.

RESULTS

Patients were diagnosed from 2009-2015. Sixty percent were male and average age at diagnosis was 58 years. Average follow-up time was 2.4 years. Ten patients had double-hit lymphoma (9 MYC/BCL2 and 1 MYC/BCL6) and nine had DLBCL with MYC translocation. Thirty patients were classified as MYC-positive by IHC. Overall survival analysis using Kaplan-Meier method, although not statistically significant, identified a trend toward the prognostic capabilities of the MYC IHC classifier. Median survival for patients MYC-negative had not been reached, whereas for patients MYC-positive, it was 6 years (log-rank $p=0.13$).

CONCLUSIONS

This study suggests that this novel MYC IHC classifier may be helpful in providing further prognostic information to improve management for DLBCL patients.

Supervisor: Dr. Anthea Peters

MOLECULAR LANDSCAPE OF ULCERATIVE COLITIS AND CROHN'S DISEASE IS CONSERVED

V. Jovanovic, J. Venner, J. Chang, P. Halloran, R. Fedorak, B.P. Halloran
Supervisor: Dr Brendan Halloran

INTRODUCTION

While disease-specific differences between IBD phenotypes are important, it is also of interest to see the conserved elements that reflect the response to injury shared by the phenotypes.

METHODS

To map the elements conserved between Ulcerative Colitis (UC) and ileal Crohn's Disease (CD) we used microarrays to study the molecular landscape of 63 UC biopsies compared to 16 control colon biopsies, and 37 ileal CD biopsies compared to 7 control ileal biopsies. These comparisons were expressed as "molecular landscapes" using volcano plots of molecular association strength via p-value (x-axis) versus fold change (y-axis). The landscape of UC (Fig 1) was compared to that of ileal CD (Fig 2) for all 13709 interquartile-range filtered probe sets. We labeled transcripts of interest, including TNFalpha, calprotectin (S100A8 and S100A9), TNFalpha-inducible transcripts, inflammasome associated transcripts, IFNG-inducible transcripts, transcripts representing the response to injury, and transcripts decreased in injured tissue (conserved epithelial genes).

RESULTS

There was striking conservation between the molecular landscape of the two disease processes. TNF-alpha was interestingly only mildly increased in UC (Fold change= 1.2, P=NS) and CD (Fold change=2.4, P=0.02) compared to controls; however calprotectin (S100A8 and S100A9) was strongly induced in both UC (P=0.0006) and ileal CD (P=0.0001) but the fold change increase in CD was higher than that induced in UC (14x vs 4x). TNFalpha-inducible and inflammasome-associated transcripts were highly conserved across both UC and CD. As expected, expression of inflammasome transcript NOD2 was only associated with CD (Fold change=2.7,P=0.003), but not in UC (P=NS). Epithelial transcripts were variably downregulated in both diseases, indicating the stereotyped dedifferentiation of the parenchyma.

CONCLUSIONS

Although one might expect UC and CD to have different inflammatory profiles as they present with markedly different phenotypes and in different epithelia, the large-scale molecular changes are strikingly conserved. Calprotectin expression was high in UC and CD in keeping with its current use as a fecal biomarker in both diseases.

Supervisor: Dr Brendan Halloran

Bilateral auricular cartilage calcification in secondary adrenal insufficiency

Anna Rogers, S. Parameswaranathan
Supervisor: Dr. Subagini Parameswaranathan

INTRODUCTION

Auricular calcification has been associated with several endocrinopathies; most commonly primary adrenal insufficiency (Addison's Disease). There have been few case reports documenting a similar presentation in secondary adrenal insufficiency.

METHODS

We describe a case of a 54-year-old male who was hemodynamically unstable at presentation and required ICU support for Group A streptococcus pharyngitis leading to septic shock complicated by mediastinitis and pericarditis. He had a history of recurrent pharyngitis requiring antibiotics and progressive fatigue over the previous year. He described a 14-year history of auricular hardening.

RESULTS

A random cortisol drawn in ICU was 617nmol/L after one dose of methylprednisone. A follow up AM cortisol level eight days later was undetectable. An ACTH stimulation test failed to show any response with undetectable cortisol levels. The ACTH level was <5ng/L. Anti-adrenal antibodies were negative. He started hydrocortisone therapy with improved energy. He had been diagnosed with TPO-negative hypothyroidism 5 years earlier with a TSH of 7.43mU/L. IGF-1, LH, FSH, prolactin, testosterone levels were normal. There was no evidence of diabetes insipidus. Imaging of the pituitary is normal.

CONCLUSIONS

Discussion: Trauma, frost bite and inflammation are the most common causes of auricular calcification. Primary adrenal insufficiency is the most frequently associated systemic condition, however it has been documented with an empty sella and panhypopituitarism. Hypercalcemia secondary to cortisol deficiency with resultant calcium deposition in the auricular cartilage has been postulated as a mechanism, however serum calcium levels are frequently normal, as in this case. The pathogenesis remains unclear. This case highlights that the differential diagnosis and investigations for auricular calcification should include assessment for both primary and secondary adrenal insufficiency.

Supervisor: Dr. Subagini Parameswaranathan

ELECTRONIC MEDICAL RECORDS IN INTERSTITIAL LUNG DISEASE: IMPLEMENTATION OF MONITORING FLOW SHEETS FOR LUNG PHYSIOLOGY

Emad Saad1, Robert Hayward1, Steven Stenson1, Tim Graham1, Nona Hait, Meena Kalluri1, Jaled Yehya1, Eric Wong1, Dilini Vethanayagam1.
Supervisor: Dr Dilini Vethanayagam

INTRODUCTION

eCLINICIAN is an enterprise ambulatory care Electronic Medical Record (EMR) system hosted by Alberta Health Services (AHS) in the Edmonton Zone for most of the last decade. Clinician leadership of clinical applications of the EMR has proved essential to engagement and benefits realization. Use of pulmonary function tests (PFT) to assess pulmonary physiology is important for effective management and monitoring of patients with interstitial lung disease (ILD). Integration of physiologic data into clinical decision-making relies upon perception of change and detection of trends. Facilitating pattern detection in large datasets can improve care through early recognition of need for therapy, evaluating response to treatment changes, personalized prognostication and targeted patient education, and engagement. A pulmonary physiology documentation flow sheet was developed, implemented, and evaluated in an effort to promote more effective decision-making by front line clinicians.

METHODS

High needs ILD patients followed by respirologists in the Kaye Edmonton Clinics (KEC) were selected using a survey and systematic consensus-building process. An electronic pulmonary physiology flow-sheet tool was developed for PFT data abstracted and entered by a nurse practitioner. A prototype was iteratively modified over a 12-month period then subjected to peer-review and optimization before implementation.

RESULTS

The eCLINICIAN pulmonary physiology flow sheet has been integrated into chronic disease management for 38 ILD patients. The time taken for PFT data abstraction averaged 5 minutes and patients averaged a total of 5 PFT sets (range 1-26). Clinicians received the tool positively and reported that it facilitated clinical decision-making.

CONCLUSIONS

Use of the pulmonary physiology electronic flow sheet for persons with ILD can potentially improve EMR workflow and clinician efficiency while improving the quality of ILD chronic disease management. A post implementation survey is underway

Supervisor: Dr Dilini Vethanayagam

Processes for Longitudinal Care of Sarcoidosis in Northern Alberta.

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Supervisor: Dilini Vethanayagam

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder that affects the lungs (90%), eyes (10-25%), liver (50-80%) heart (5% symptomatic but at lease 25% in autopsy studies), and brain (10%) leading to dire consequences if not adequately monitored in a longitudinal and comprehensive manner. The Sarcoid Study was initiated at the University of Alberta to assess and describe the management of sarcoid patients in Northern Alberta. Evaluating systems of care in Alberta is part of the mandate of this project.

METHODS

Prospective observational study of patients recruited from different adult specialist clinics based of the University of Alberta Hospital. Inclusion criteria were adults greater than 17 years old with a biopsy-confirmed diagnosis of Sarcoidosis or patients with Lofgren’s syndrome who didn’t have a biopsy confirmation. Assessment of process for evaluation and longitudinal monitoring were evaluated.

RESULTS

A total of 30 subjects have been recruited thus far. Mean duration of disease diagnosis was 6.4 years. 28 (93%) had Family Physicians (all of the family physicians were part of a primary care network). Pulmonary function tests were done in 30 (100%). Electrocardiography was done in 26 (87%) and echocardiogram was done in 15 (50%). Only 19 subjects (63%) had seen an ophthalmologist and 2 of them had ocular involvement.

CONCLUSIONS

The goal of Sarcoidosis management is to prevent or control organ damage. Yet, standard practice for evaluation and monitoring of sarcoid patients is not well defined. Although patients had good access to primary care physicians, ECG, echocardiogram and Ophthalmology consult were only done in some of them, yet it is essential in Sarcoidosis work up. Update of the current guidelines to standardize the work up and monitoring strategies is urgently needed.

Supervisor: Dr. Dilini Vethanayagam

Adherence to cardiac surgical waitlist guidelines is a poor predictor of cardiac surgery waitlist mortality

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Supervisor: Dr. Sean van Diepen

INTRODUCTION

Cardiac surgery waitlist recommendations which were developed based on expert opinion and cardiac structural information poorly predict pre-operative cardiac events. Studies reporting the risk factors for waitlist mortality are limited by unreported measures of model performance and have not evaluated the incremental risk associated with non-adherence to waitlist recommendations.

METHODS

In a provincial population-based dataset we identified 12,464 patients ≥18 years old referred for cardiac surgery between 2009 and 2015. Logistic regression was used to identify independent predictors of cardiac surgical waitlist mortality. Model discrimination was assessed with a c-index and calibration with the Hosmer-Lemeshow test.

RESULTS

A total of 101 (0.8%) patients died awaiting cardiac surgery. The median wait-times and frequency of waitlist deaths among patients undergoing emergent, urgent, semi-urgent, and non-urgent surgery were 0.6, 7.3, 69.0, 56.3 days ($p<0.001$) and 6.3%, 0.8%, 0.3%, 0.5% ($p<0.001$) respectively. Non-adherence to Canadian Cardiovascular Society waitlist recommendations showed a trend of being higher among waitlist deaths (53.5% vs 47.2%, $p=0.207$) and was a poor univariable predictor of waitlist mortality (odds ratio 1.29, 95% CI 0.87-1.91; c-index=0.530). After multivariable adjustment, 10 variables (Table 1) were independently associated with cardiac surgical waitlist mortality. The present model (c-index=0.854, Hosmer-Lemeshow $p=0.788$) compares favourably in its ability to discriminate waitlist mortality compared to current CCS guidelines (Figure 1).

CONCLUSIONS

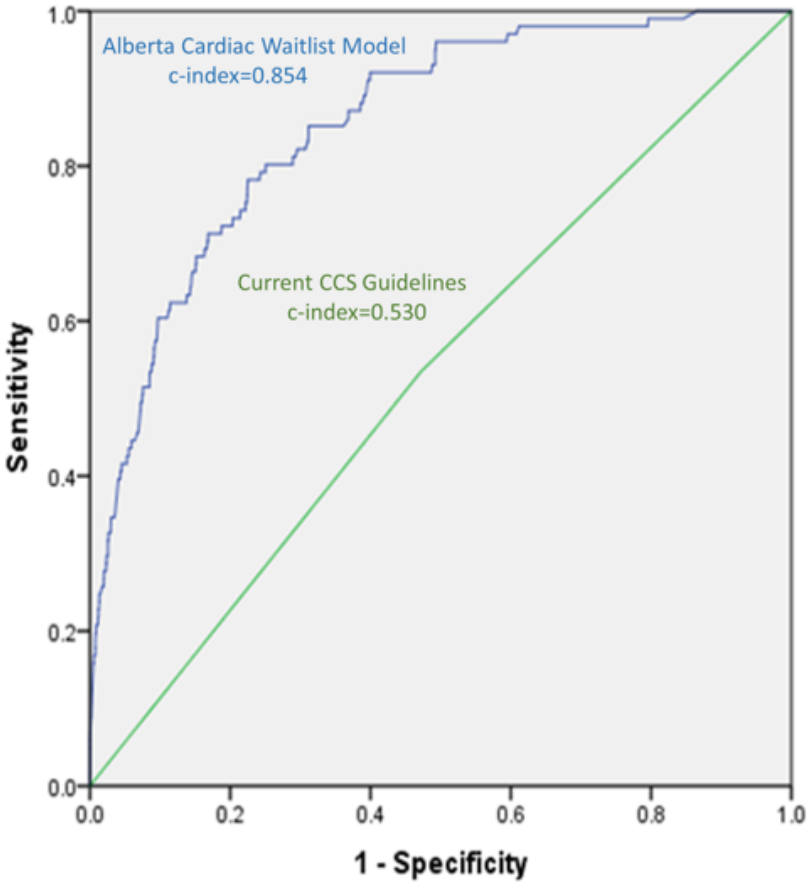
In a large population-based provincial cohort, we observed that adherence to cardiac surgical waitlist recommendations alone was poorly predictive of waitlist mortality. We derived a clinical prediction model with excellent discrimination and calibration that incorporates pre-operative clinical and cardiac structural variables with existing guidelines. Our findings suggest a need to re-evaluate cardiac surgical triage criteria and implement a more evidence-based approach toward preventing waitlist mortality.

Supervisor: Dr. Sean van Diepen

Table 1. Variables independently predictive of cardiac surgical waitlist mortality.

Variable	OR	95% CI
Emergent surgery	15.82	8.39-28.81
EF not done due to instability in cath lab	2.47	1.27-4.77
Urgent Surgery	2.55	1.46-4.45
Aortic surgery	2.08	1.08-4.02
Non adherence to guidelines	3.22	2.01-5.17
Ejection fraction <35%	2.67	1.15-6.20
Heart failure	2.32	1.38-3.88
Chronic pulmonary disease	0.45	0.25-0.79
Hypertension	0.41	0.26-0.65
Dyslipidemia	0.32	0.20-0.52

Figure 1. Receiver operating characteristic curve of the Alberta cardiac surgical waitlist model and current CCS guidelines for cardiac surgical waitlist mortality.



COMPARATIVE OUTCOMES AMONG CLOPIDOGREL, PRASUGREL, AND TICAGRELOR IN ST ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION; INSIGHTS FROM THE TOTAL TRIAL

Robinder S. Sidhu, John Cairns, Shahar Lavi, Sasko Kedev, Raul Moreno, Warren Cantor, Goran Stankovick, Brandi Meecks, Fei Yuan, Vladimir Dzavik, Sanjit Jolly, Robert C Welsh
Supervisor: Dr. Robrert C. Welsh

INTRODUCTION

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

METHODS

The TOTAL trial (ThrOmbecTomy with PCI versus PCI ALone in patients with STEMI undergoing primary PCI) randomized 10,02 patients. For this post hoc analysis, patients were grouped based on P2Y12 inhibitor use: Clopidogrel (C) (n=6500), Prasugrel (P) (n=1244), or Ticagrelor (T)(n=2188). The primary outcome was the one year composite of CV death, recurrent MI, cardiogenic shock, or NYHA Class IV heart failure. Secondary ischemic outcomes and major bleeding events were assessed.

RESULTS

Baseline characteristics were similar between groups with the exception that Prasugrel patients were less likely to be >75yo (P5.5%, C14.5%, T11.6%) or have prior stroke (P0.7%, C3.7%, T2.2%) but had higher rates of diabetes (P20.3%, C18.8%, T15.2%). The primary composite outcome was significantly lower with Ticagrelor compared to Clopidogrel (T4.8% - C8.6%; HR 0.55 (0.41-0.96)) but not with Prasugrel (P1.6%, C1.8%, HR 0.88 (0.55-1.41)). Further adjusted analysis and Prasugrel/Ticagrelor comparison will be completed prior to the presentation.

CONCLUSIONS

In STEMI with PPCI, Ticagrelor was associated with a significantly lower rate of the composite outcome and mortality at 1 year, as well as fewer major bleeds than Clopidogrel. Prasugrel was associated with a trend to fewer primary outcome events and no more major bleeding than Clopidogrel. This unadjusted post hoc analysis supports these agents in preference to Clopidogrel in the setting of PPCI.

Supervisor: Dr. Robrert C. Welsh

Understanding unnecessary lab testing on internal medicine wards

Inka Toman, Pam Mathura and Narmin Kassam
Supervisor: Dr. Narmin Kassam

INTRODUCTION

The Canadian Choosing Wisely campaign recommends against routine complete blood count (CBC) and chemistry testing in the face of clinical stability in the inpatient internal medicine setting. At the University of Alberta Hospital (UAH), we hypothesized that overutilization of lab tests on the internal medicine wards is a problem.

METHODS

Our goal was to understand this problem by analyzing lab data, performing a chart audit, surveying residents about lab overutilization, and mapping the process of lab ordering.

RESULTS

Analysis of six months of lab data showed that CBC, electrolytes, creatinine and urea accounted for more than 50% of all lab tests performed. A chart audit showed that most patients have daily lab tests ordered at admission and daily lab testing is often bundled. In a survey of internal medicine residents regarding lab test ordering patterns, residents admitted to frequently ordering unnecessary lab tests – the primary reason for this being department culture. Through process mapping we learned that physicians are often unaware when patients are getting daily lab tests, and do not have a formal process to review inpatient lab orders. Conversely, the unit clerk records which patients are scheduled to have daily lab tests, but does not have a formal process to communicate this information to the physicians.

CONCLUSIONS

Culture and communication gaps are major driving forces behind lab overutilization on UAH internal medicine wards. By involving relevant stakeholders to help understand the problem, we have implemented a multifaceted ‘plan-do-study-act’ cycle on one internal medicine unit consisting of education and process change.

Supervisor: Dr. Narmin Kassam

Nine Year Trends in Cause-Specific Mortality after Percutaneous Coronary Intervention (PCI): Observations from the Alberta Provincial Project for Outcome assessment in Coronary heart disease (APPROACH) Registry

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Supervisor: Dr. Roopinder Sandhu

INTRODUCTION
Nowadays, percutaneous coronary intervention (PCI) patients are older with higher comorbidities, yet data examining trends in cause-specific mortality are sparse.

METHODS
Prospective cohort study using APPROACH which collects data on patients undergoing angiograms in Alberta, determining cause-specific mortality based on death certificates, for patients > 20 years undergoing PCI from 2005-2013. Administrative codes (ICD-10) were used to classify deaths into all-cause, cardiac and non-cardiac mortality at different time points including 30 days, 1 and 2 years. The primary endpoint was the proportion of cardiac versus non-cardiac deaths 12 months after PCI.

RESULTS
Study population was 35,602; mean age was 62.9 11.9 years, and 23.4% were female. More patients undergoing PCI had an indication of STEMI or NSTEMI ($p<0.001$). A significant increasing trend of overall and cardiac mortality during the study was seen. Kaplan-Meier curves after PCI (10-year follow up), reveals cardiac mortality dominating the mode of death, plateauing at 4 years; whereas, non-cardiac deaths continue to rise becoming the leading cause of death. Predominant mode of death was cardiac within 2 years after PCI (cardiac: within first month=83%, 30 days to 1 year= 64%, 1 to 2 years=55%; non-cardiac: within first month=12%, 30 days to 1 year=32%, 1 year to 2 years=40%), with a decline in cardiac and an increase in non-cardiac causes, as time from the PCI increased, p0.001). Clinical characteristic of survivors versus non-survivors after PCI shows deceased patients were more likely to have hypertension and heart failure. NSTEMI patients tend to die from non-cardiac causes.

CONCLUSIONS
Although demographics of PCI patients have changed, non-cardiac mortality rates have not significantly altered over years. On the other hand, all-cause mortality has increased due to the drastic rise in cardiac deaths.

Supervisor: Dr. Roopinder Sandhu

Table 1: Characteristics and mortality of study population at index PCI (First PCI)

Variable	All	2005	2006	2007	2008	2009	2010	2011	2012	2013	p
N patient	35,602	3,906	3,829	3,616	3,821	3,836	4,037	4,143	4,139	4,275	
Age (years), mean (SD)	62.6 (11.9)	62.2 (11.9)	62.2 (11.7)	62.1 (11.9)	62.5 (11.9)	62.7 (12)	62.4 (11.9)	62.5 (11.8)	63 (12.1)	63.5 (12)	<0.001
Female (%)	23.4	25.3	22.6	23.9	23	23	21.4	22.2	25.7	23.6	0.676
Cardiovascular Comorbidities (%)											
Hypertension	69.1	67	67.5	69.6	68.9	69.9	71	69.5	69.7	68.8	0.007
Hyperlipidemia	71	79.5	77.3	72.5	71.7	69.9	70.5	67	66.4	65.8	<0.001
Diabetes mellitus	25	23.9	23.9	24.5	23.9	26	25.4	26.2	24.9	26.5	0.001
Renal disease	4	4.1	4	3.9	4.2	4	3.8	4.2	4.1	3.8	0.805
Heart failure	8.3	9.4	8.1	8.8	10.2	8.3	8.1	7.2	7.2	7.3	<0.001
Prior MI	16.2	20.7	20.4	17.3	17.1	16.7	14.2	14.3	12.4	13.2	<0.001
Peripheral vascular disease	9.8	6.3	6.2	5.8	11	11.6	11.7	12.4	11.3	11.1	<0.001
Repeat PCI within 90 days	8.1	7.7	7.1	7.4	7.9	7.7	8	8.4	9.5	8.9	<0.001
Indication for catheterization (%)											
STEMI	33	30.7	31.2	32.9	32.2	32.4	34.1	34.3	34.8	34.1	<0.001
NSTEMI	28.6	20.3	27.8	30.2	29.8	29.6	28.6	30.3	29.9	30.8	<0.001
Unstable Angina	12	15.6	13.7	11.6	12.6	12	11.2	10.2	10.3	10.8	<0.001
Stable Angina	20.3	21.3	21.8	18.8	20	21.2	20.6	20.5	19.3	19.4	0.019
Total mortality (%)											
30-day	2.1	1.5	1.8	2.1	2.1	1.9	2.6	2.3	2	2.7	0.001
1-year	4.2	3.3	3.6	3.9	4.1	3.9	4.8	4.5	4.3	5.1	<0.001
2-year	6	5.2	5.1	5.6	5.6	6.1	6.7	6	6.3	6.9	<0.001
Cardiac mortality (%)											
30-day	1.8	1.2	1.6	1.7	1.8	1.6	2.1	1.8	1.6	2.4	0.001
1-year	2.7	1.8	2.5	2.4	2.6	2.3	3.1	2.7	2.6	3.6	<0.001
2-year	3.3	2.6	3.1	3	3.1	3.2	3.9	3.4	3.2	4.2	<0.001
Non-cardiac mortality (%)											
30-day	0.3	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.2	0.684
1-year	1.3	1.3	1	1.3	1.3	1.4	1.4	1.6	1.5	1.3	0.154
2-year	2.4	2.3	1.9	2.3	2.3	2.7	2.5	2.3	2.7	2	0.531

SD: standard deviation; MI: Myocardial infarction; STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction.

Home or hospital? Trends and predictors of location of death among patients with heart failure and acute coronary syndromes

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Supervisor: Dr. Justin A. Ezekowitz

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

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

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

CONCLUSIONS
Approximately 40% of deaths after HF or ACS hospitalizations occur OOH. The reasons for the sustained high proportion of acute care hospital deaths in patients with HF require further investigation.

Supervisor: Dr. Justin A. Ezekowitz

Table 1: Baseline characteristics of the study population.

Variable	Statistic	ACS	HF	P-value
Total N	N	55515	30279	
Female gender	n (%)	17644 (31.8)	15422 (50.9)	<0.01
Age, y				
	Mean (SD)	65.8 (13.8)	77.3 (12.5)	<0.01
	Median (IQR)	65.0 (55.0, 77.0)	80.0 (70.0, 86.0)	<0.01
Age, y				<0.01
< 65	n (%)	26524 (47.8)	4650 (15.4)	
65-74	n (%)	12491 (22.5)	5740 (19.0)	
≥ 75	n (%)	16500 (29.7)	19889 (65.7)	
Urban residence at time of hospitalization				<0.01
	n (%)	44064 (79.4)	23117 (76.3)	
Median household income				<0.01
≤ $52161	n (%)	11658 (21.0)	7624 (25.2)	
$52162-$58598	n (%)	14271 (25.7)	8432 (27.8)	
$58599-$69710	n (%)	14359 (25.9)	7953 (26.3)	
≥ $69711	n (%)	15227 (27.4)	6270 (20.7)	
Duration of disease, y**				<0.01
no	n (%)	41663 (75.0)	10502 (34.7)	
< 1	n (%)	2113 (3.8)	4693 (15.5)	
1-5	n (%)	3520 (6.3)	6412 (21.2)	
≥ 5	n (%)	8219 (14.8)	8672 (28.6)	
Comorbidities				
Acute coronary syndrome*	n (%)	13852 (25.0)	10775 (35.6)	<.0001
Heart failure*	n (%)	8380 (15.1)	19777 (65.3)	<.0001
Atrial fibrillation or flutter	n (%)	7579 (13.7)	15657 (51.7)	<.0001
Hypertension	n (%)	39734 (71.6)	25349 (83.7)	<.0001
Diabetes	n (%)	15587 (28.1)	11984 (39.6)	<.0001
Renal disease	n (%)	4837 (8.7)	8066 (26.6)	<.0001
Peripheral vascular disease	n (%)	6313 (11.4)	6129 (20.2)	<.0001
Cerebrovascular disease	n (%)	7160 (12.9)	7510 (24.8)	<.0001
Dementia	n (%)	2173 (3.9)	3831 (12.7)	<.0001
COPD	n (%)	15071 (27.1)	16340 (54.0)	<.0001
Cancer	n (%)	5807 (10.5)	5713 (18.9)	<.0001
Charlson score				
0	n (%)	17660 (31.8)	1624 (5.4)	<.0001
1,2	n (%)	18075 (32.6)	6868 (22.7)	
3,4	n (%)	10624 (19.1)	8114 (26.8)	
5 or higher	n (%)	9156 (16.5)	13673 (45.2)	

Table 3: Location of death at 1 year post-discharge in HF group

	# pts N	Mortality n (% of N)	Acute** hospital (% of n)	Non-acute** hospital (% of n)	ED (% of n)	Out of hospital/ED (% of n)	p*
Overall	24237	6162 (25.4)	3531 (57.3)	191 (3.1)	130 (2.1)	2310 (37.5)	
Sex							0.04
F	12341	3131 (25.4)	1769 (56.5)	103 (3.3)	46 (1.5)	1213 (38.7)	
M	11896	3031 (25.5)	1762 (58.1)	88 (2.9)	84 (2.8)	1097 (36.2)	
Age							<0.01
< 65	3996	494 (12.4)	285 (57.7)	7 (1.4)	20 (4.0)	182 (36.8)	
65-74	4817	924 (19.2)	598 (64.7)	19 (2.1)	30 (3.2)	277 (30.0)	
≥ 75	15424	4744 (30.8)	2648 (55.8)	165 (3.5)	80 (1.7)	1851 (39.0)	
Residence							<0.01
Rural	5923	1488 (25.1)	932 (62.6)	19 (1.3)	48 (3.2)	489 (32.9)	
Urban	18314	4674 (25.5)	2599 (55.6)	172 (3.7)	82 (1.8)	1821 (39.0)	
MHI							0.04
≤ $52161	6162	1594 (25.9)	877 (55.0)	64 (4.0)	31 (1.9)	622 (39.0)	
$52162-$58598	6895	1771 (25.7)	1049 (59.2)	41 (2.3)	49 (2.8)	632 (35.7)	
$58599-$69710	6315	1614 (25.6)	961 (59.5)	38 (2.4)	32 (2.0)	583 (36.1)	
≥ $69711	4865	1183 (24.3)	644 (54.4)	48 (4.1)	18 (1.5)	473 (40.0)	
Duration of disease***							0.65
no	8412	1632 (19.4)	908 (55.6)	54 (3.3)	38 (2.3)	632 (38.7)	
< 1 year	3747	936 (25.0)	549 (58.7)	23 (2.5)	22 (2.4)	342 (36.5)	
1-5 years	5240	1513 (28.9)	875 (57.8)	43 (2.8)	29 (1.9)	566 (37.4)	
≥ 5 years	6838	2081 (30.4)	1199 (57.6)	71 (3.4)	41 (2.0)	770 (37.0)	

*p-values compare the frequency of out of hospital deaths among deaths across characteristic strata
**Acute hospitals were considered only those teaching or community hospitals listed in 2014_15 CIHI file. Acute status refers to hospitalization where death occurred
***Beginning of disease was searched in any diagnosis fields of DAD (April 1, 1994), ACCS (April 1, 1997), CLAIMS (OFFC April 1, 1994)

Table 2: Location of death at 1 year post-discharge in ACS group

	# pts N	Mortality n (% of N)	Acute** hospital (% of n)	Non-acute** hospital (% of n)	ED (% of n)	Out of hospital/ED (% of n)	p*
Overall	47700	3135 (6.6)	1902 (60.7)	84 (2.7)	108 (3.4)	1041 (33.2)	
Sex							0.8
F	15043	1276 (8.5)	778 (61.0)	39 (3.1)	32 (2.5)	427 (33.5)	
M	32657	1859 (5.7)	1124 (60.5)	45 (2.4)	76 (4.1)	614 (33.0)	
Age							<0.01
< 65	23211	409 (1.8)	209 (51.1)	7 (1.7)	32 (7.8)	161 (39.4)	
65-74	10792	588 (5.4)	397 (67.5)	8 (1.4)	21 (3.6)	162 (27.6)	
≥ 75	13697	2138 (15.6)	1296 (60.6)	69 (3.2)	55 (2.6)	718 (33.6)	
Residence							<0.01
Rural	9945	661 (6.6)	439 (66.4)	15 (2.3)	36 (5.4)	171 (25.9)	
Urban	37755	2474 (6.6)	1463 (59.1)	69 (2.8)	72 (2.9)	870 (35.2)	
MHI							0.41
≤ $52161	10025	816 (8.1)	508 (62.3)	19 (2.3)	17 (2.1)	272 (33.3)	
$52162-$58598	12321	804 (6.5)	478 (59.5)	23 (2.9)	33 (4.1)	270 (33.6)	
$58599-$69710	12415	790 (6.4)	497 (62.9)	13 (1.6)	35 (4.4)	245 (31.0)	
≥ $69711	12939	725 (5.6)	419 (57.8)	29 (4.0)	23 (3.2)	254 (35.0)	
Duration of disease***							0.67
no	35550	1922 (5.4)	1153 (60.0)	57 (3.0)	63 (3.3)	649 (33.8)	
< 1 year	1870	183 (9.8)	118 (64.5)	5 (2.7)	6 (3.3)	54 (29.5)	
1-5 years	3204	338 (10.5)	202 (59.8)	10 (3.0)	13 (3.8)	113 (33.4)	
≥ 5 years	7076	692 (9.8)	429 (62.0)	12 (1.7)	26 (3.8)	225 (32.5)	

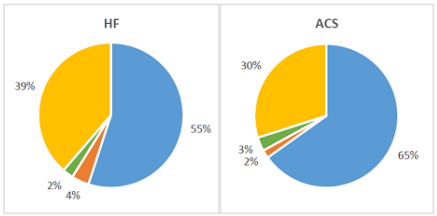
*p-values compare the frequency of out of hospital deaths among deaths across characteristic strata
**Acute hospitals were considered only those teaching or community hospitals listed in 2014_15 CIHI file. Acute status refers to hospitalization where death occurred
***Beginning of disease was searched in any diagnosis fields of DAD (April 1, 1994), ACCS (April 1, 1997), CLAIMS (OFFC April 1, 1994)

Table 4: Multivariable model for location of death of patients who died within 1 year since discharged alive from index hospitalization

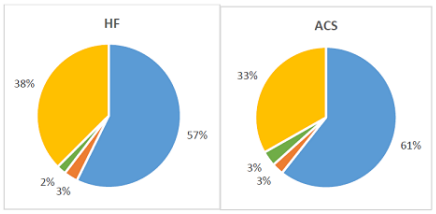
	ACS (N=3135)			HF (N=6162)		
	OR for out of hospital death	95% CI	p	OR for out of hospital death	95% CI	p
Male gender	0.98	(0.84 , 1.15)	0.8164	0.93	(0.84 , 1.03)	0.1857
Age, reference < 65 years						
65-74	0.59	(0.45 , 0.77)	0.0001	0.75	(0.59 , 0.94)	0.0139
75+	0.77	(0.61 , 0.96)	0.0204	1.09	(0.90 , 1.32)	0.3848
Urban residence, reference rural residence	1.84	(1.46 , 2.32)	<.0001	1.28	(1.11 , 1.48)	0.0008
MHI reference ≤ $52161						
$52162-$58598	1.34	(1.06 , 1.70)	0.0133	0.98	(0.84 , 1.14)	0.763
$58599-$69710	0.93	(0.76 , 1.15)	0.5274	0.89	(0.77 , 1.03)	0.1286
≥ $69711	1.01	(0.82 , 1.25)	0.8976	1.02	(0.87 , 1.19)	0.8178
Duration of disease, reference incident patients						
< 1 year	0.81	(0.57 , 1.13)	0.2132	0.94	(0.80 , 1.12)	0.5091
1-5 years	0.97	(0.75 , 1.25)	0.8259	0.98	(0.84 , 1.14)	0.8227
5+ years	0.95	(0.78 , 1.16)	0.6092	0.97	(0.84 , 1.11)	0.6395
Charlson score, reference 0						
1,2	0.94	(0.69 , 1.28)	0.6787	0.88	(0.61 , 1.27)	0.4941
3,4	0.99	(0.73 , 1.35)	0.9715	0.8	(0.56 , 1.15)	0.2244
5 or higher	1.01	(0.75 , 1.37)	0.9304	0.79	(0.55 , 1.14)	0.2068

Figure 1: Comparison of location of death at 90 days, 1 year and 5 years post-discharge from HF and ACS hospitalizations

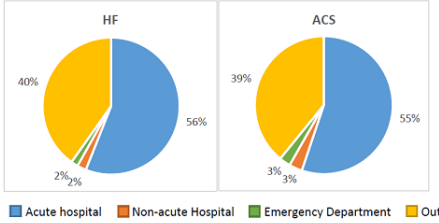
A. 90 days post-discharge



B. 1 year post-discharge



C. 5 years post-discharge



Acute hospital | Non-acute Hospital | Emergency Department | Out of Hospital

Thiopurine Metabolite Levels in the Optimization of Thiopurine Therapy in IBD

J. Zhu, J. Abraldes, L. Dieleman, V. Huang, K. Kroeker, F. Peerani, K. Wong, D. LeGatt, R. Fedorak, B. Halloran
Supervisor: Dr. B. Halloran

INTRODUCTION

About 30-50% of active IBD fail to respond to conventional weight-based dosing regimens of thiopurine therapy. Studies suggest 6-TG and 6-MMP levels are better therapeutic targets in these patients. The objectives of the study were to assess thiopurine metabolite levels, physician response to thiopurine metabolite levels, and how they altered IBD therapy and patient outcomes.

METHODS

Thiopurine metabolite levels were obtained retrospectively from a chart review of 159 adult IBD patients between 2014 and 2015. Objective clinical outcomes were examined.

RESULTS

The mean 6-TG level was 443.4 pmol/8x108 RBC and mean 6-MMP level was 3690.5 pmol/8x108 RBC. Mean 6-MMP to 6-TG ratio was 10.9 (95% CI: 8.8-13.0). The primary indication for assessing metabolite levels was sub-therapeutic response followed by thiopurine intolerance. Concordance rate between sub-therapeutic 6-TG levels and sub-clinical response was 59%. Concordance between 6-MMP level and liver toxicity was poor. Overall trend in AZA dose escalation did not lead to incremental increase of 6-TG (Fig1). In 5 patients, metabolite levels were re-measured post addition of allopurinol; there was reduction of 6-MMP and increased 6-TG level post allopurinol use and none developed side effects (Tab1).

CONCLUSIONS

In patients who failed to respond to weight based thiopurine dosing regimen, assessing thiopurine metabolite levels led to individualized and optimized thiopurine therapy in IBD patients. The utilization of allopurinol may be a safe alternative to those who do not response to standard weight-based dosing. The optimal interval of serial metabolite monitoring remains to be determined.

Supervisor: Dr. B. Halloran

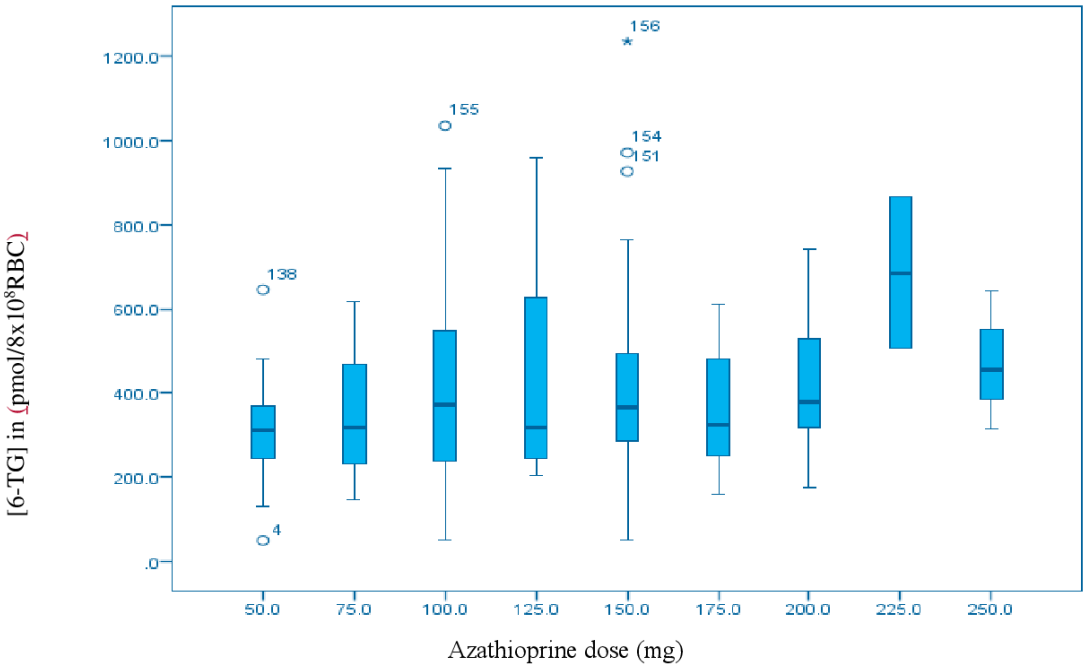


Figure 1: Boxplot of 6-TG levels in relation to azathioprine doses.

Table 1. Metabolite Levels Pre and Post Allopurinol in 5 IBD Patients and Outcomes

		AZA (mg)	Allopurinol (mg)	Other IBD Drugs	6-TGN Level*	6-MMP Level*	mHBI/p Mayo	Outcome
Case 1: UC Pancolitis	Pre	100	0	Anti-TNFα+ Pred	173	7942	5	
Sub-therapeutic response	Post	100	100	Anti-TNFα	451	350	0	Clinical remission
Case 2: CD Colonic Dz	Pre	200	0	None	221	10422	2	
Others	Post	50	100	None	152	350	0	Clinical remission
Case 3: CD Ileocolonic Dz	Pre	150	0	Anti-TNFα + 5-ASA	206	14023	0	
Transaminase elevation	Post	25	100	Anti-TNFα + 5-ASA	421	431	0	Normalized liver enzymes
Case 4: CD Ileal Dz	Pre	200	0	None	222	12904	6	
Sub-therapeutic response	Post	25	100	Anti-TNFα	281	350	0	Clinical remission
Case 5: UC Pancolitis	Pre	200	0	Anti-TNFα + 5-ASA	236	1810	0	
Others	Post	100	100	Anti-TNFα + 5-ASA	646	350	0	Clinical remission

Sleep Quality in Patients with Inactive Inflammatory Bowel Disease Reporting Fatigue

Candace Beilman (1), Alexandra Dittrich (1), Holly Scott (2), Brian McNab (1), Karen Kroeker (1)
Supervisor: Dr. Karen Kroeker

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal tract. Fatigue is a common symptom of IBD, and presents in higher proportions of IBD patients compared to the general population, even in periods of disease remission. Studies have suggested that altered sleeping patterns may be associated with the fatigue experienced by this patient population. The aim of this study was to objectively assess the prevalence of sleep disturbance in patients with inactive IBD experiencing fatigue.

METHODS

We conducted a prospective observational pilot study examining IBD outpatients, who had inactive disease and experienced chronic fatigue. Patients' sleep was assessed for one night using polysomnography (PSG) at a Level One sleep clinic. Patients completed 3 validated questionnaires to assess fatigue, depression levels, and sleep quality: 1) Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), 2) Beck Depression Inventory-II (BDI-II), and 3) Pittsburgh Sleep Quality Index (PSQI). Scores were then compared to published scores of the general public.

RESULTS

Demographic characteristics are shown in Table 1. IBD patients slept an average of 377.0 minutes, with an average sleep efficiency of 83.0%. Mild obstructive sleep apnea was experienced in 3/13 (23.1%) patients enrolled. Periodic limb movement was seen in 5/13 (38.5%) of patients. IBD patients had a mean FACIT-F score of 29.1, significantly lower than the general population score of 43.6 ($p<0.0001$), indicating increased fatigue levels. IBD patients scored an average of 7.9 on the PSQI and 13.2 on the BDI-II, significantly higher than the average population score of 3.2 ($p<0.0001$) and 7.8 ($p=0.016$), respectively.

CONCLUSIONS

PSG results of IBD patients showed high rates of sleep apnea and periodic limb movement, although more patient data is needed to make robust conclusions. Subjective levels of fatigue and depression were higher, and subjective quality of sleep was lower in IBD patients compared to the general population.

Supervisor: Dr. Karen Kroeker

Table 1. Demographic characteristics of participants.

Characteristics	Participants (n=13)
Disease Type (% CD)	46.2%
Gender (% Female)	76.9%
Age (yrs ± SD)	35.5 ± 10.5
Fecal Calprotectin (µg/g ± SD)	109.5 ± 87.7
BMI (kg/m^2 ± SD)	25. ± 5.4

Cost-Effectiveness of Infliximab Biosimilar for the Management of Crohn's Disease

Candace Beilman (1), Christopher Ma (2), Christopher McCabe (1), Richard Fedorak (1), Brendan Halloran (1)
Supervisor: Dr. Brendan Halloran

INTRODUCTION

Infliximab is an anti-TNFα therapy with proven efficacy for the induction and maintenance of remission in patients with Crohn’s disease (CD). An infliximab biosimilar, CT-P13 (marketed as Inflectra), has recently been introduced that could potentially result in large cost-savings for this patient population due to its lower price. However, the molecular complexity and sensitivity to changes in manufacturing of biologic agents makes it difficult to verify the similarity of biosimilars to their respective originator biologics. The aim of this study was to provide an economic analysis comparing the cost-effectiveness of infliximab (Remicade) to its biosimilar CT-P13 (Inflectra) for the management of CD.

METHODS

A Markov model was constructed to simulate the progression of patients with CD after initiating either infliximab or its biosimilar, CT-P13. Based on this model, we calculated the cost and effectiveness of each treatment strategy over a 5-year time horizon. Transition probabilities were obtained from a literature search, and loss of response rates were obtained from centre data and observational studies. The cost of health states were accessed using the CIHI patient cost estimator, and the costs of Remicade and Inflectra were obtained from the Alberta Health and Wellness Drug Benefit List. Utility values were obtained from a literature search, and sensitivity analysis was performed to characterize uncertainty.

RESULTS

Originator infliximab therapy costs patients with CD $167,388 and yielded 3.91 quality-adjusted life years (QALYs). Infliximab’s biosimilar costs patients $111,981 and yielded 3.61 QALYs. At a willingness-to-pay threshold of $50,000 per QALY, infliximab’s biosimilar CT-P13 had a 91% chance of being cost-effective, whereas originator infliximab had a 9% chance of being cost-effective.

CONCLUSIONS

Infliximab’s biosimilar CT-P13 resulted in large cost reductions despite similar effectiveness to innovator infliximab for patients with CD. Based on these results, the introduction and mainstream usage of CT-P13 may help reduce the economic burden associated with CD.

Supervisor: Dr. Brendan Halloran

Occupational/Environmental Exposures in Sarcoidosis in Alberta

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Supervisor: Dr. Dilini Vethanayagam

INTRODUCTION

Sarcoidosis is a multi-organ disease which has been reported to occur at a higher prevalence in Alberta than many other health jurisdictions in and outside of Canada. There has been little success in identifying exposure risks that may lead to sarcoidosis, although beryllium exposure has been shown to cause an identical disease. The purpose of our study was to identify patterns in occupational or environmental exposures among patients with sarcoidosis in Alberta.

METHODS

Methods: A prospective observational study was done at the University of Alberta Hospital. Patients with sarcoidosis, stages 1-4, were recruited from specialty clinics (Respirology, Cardiology, Neurology and Occupational Health). A predetermined list of industries thought to involve potentially relevant exposures for the development of sarcoidosis was used to capture current and previous exposure history. Researchers drew information directly from subjects via interview and from documented clinical interviews in e-charts.

RESULTS

A total of 30 subjects were recruited, 20(67%) men and 10(33%) women.
Self-identified exposure history results were as follows:
9(30%) oil and gas; 8(26%) farming or other agricultural work; 7(23%) metal working; 6(20%) construction; 5(17%) animal handler/veterinarian; 4(13%) asbestos exposure; 3(10%) mining; 3(10%) exposure to pepper spray; 3(10%) stone, clay, concrete; 3(10%) health care sector; 3(10%) lumber and wood products; 3(10%) repairing electrical equipment; 2(7%) manufacturing of industrial equipment; 2(7%) chemical industry; 2(7%) manufacturing of automotive electrical equipment; 2(7%) repairing/rebuilding of non-electrical vehicle parts; 2(7%) metal industry; 1(3%) pulp and paper; 1(3%) manufacturing of heating equipment; 1(3%) armed forces; 1(3%) firefighting.

CONCLUSIONS

Among this cohort of subjects, 87% reported working with a potentially relevant industry exposure- the largest being oil and gas (30%), and farming and agricultural work (26%). During clinic encounters, detailed evaluations of exposures within these job types are essential, taking into account duration, dose, and toxicity of exposure.

Supervisor: Dr. Dilini Vethanayagam

CURRENT CAPACITY FOR KIDNEY CARE: HOW DOES CANADA COMPARE TO OTHER OECD COUNTRIES?

Lunney M(1), Ye F(2), Wiebe N(2), Rateb A(2), Osman M(2), Johnson D(3), Tonelli M(4), Levin A(5), Bello AK(2)
Supervisor: Dr. Aminu Bello

INTRODUCTION

Background:
As part of the International Society of Nephrology (ISN) “Closing the Gap Initiative”, a multinational survey was conducted to better understand the current capacity for kidney care for patients with chronic kidney disease (CKD) and acute kidney injury (AKI) around the globe,
Objectives:
This study examines where Canada stands in relation to other countries in the Organization for Economic Cooperation (OECD) with respect to healthcare coverage, workforce capacity, medication access, registries, and advocacy.

METHODS

A survey was developed by the ISN with support of local leaders. During May to September 2016, key stakeholders in nephrology across 125 countries completed the survey. Responses were analyzed using descriptive statistics.

RESULTS

Respondents from 25 OECD countries participated in the survey. Density of nephrologists and trainees was lower in Canada relative to all OECD countries (Table 1). No shortages of healthcare providers were identified in Canada except for primary care physicians, which were also identified in 50% of OECD countries. Dietitians, renal pathologists, social workers, vascular access coordinators, and dialysis nurses were lacking in over 60% of all countries. Nephrologists were short in 42% of countries. Canada funded medication for kidney disease patients through a mix of public and private sources. The majority of OECD countries funded medication through public funding. Only 2 countries have a registry for non-dialysis CKD and 5 countries reported that CKD is recognized as a health priority by their government. Canada reported no registry and no advocacy as a top health priority for government.

CONCLUSIONS

This survey provides useful information on Canada’s level of capacity for providing kidney care, relative to all OECD countries. Further work is needed to understand why Canada is behind most OECD nations on workforce and training capacity, and coverage of medications for CKD patients through public funding.

Supervisor: Dr. Aminu Bello

Table 1. Nephrologist and nephrology trainee densities in Canada and all OECD countries.

		Nephrologists (pmp)	**Nephrology Trainees** (pmp)
Canada		17.81	2.14
OECD	Mean (SD)	23.59 (15.1)	4.79 (6.8)
	Median	20.51	2.84
	Range	6.3 – 78.79	0.1 – 35.46

pmp = per million population

AN EDUCATIONAL WEB PORTAL IMPROVES CONCERNS OF INFLAMMATORY BOWEL DISEASE PATIENTS REGARDING PREGNANCY AND MEDICATION

Reed Sutton, Kelsey Wierstra, Lindsy Ambrosio, Levinus Dieleman, Brendan Halloran, Karen Kroeker, Richard Fedorak, Karen Wong, Keri-Ann Berga, Vivian Huang
Supervisor: Dr. Vivian Huang

INTRODUCTION

Inflammatory bowel disease (IBD) and IBD therapies can affect pregnancy outcomes, however most women with IBD can have healthy pregnancies. Almost 50% of women with IBD have poor reproductive knowledge, which has been associated with unsubstantiated concerns. To address these, we developed and evaluated an educational web portal for the improvement of IBD patients' reproductive and medication concerns.

METHODS

We designed a web portal (Pixel Designs Company) with educational modules that covers heritability, fertility, surgery, pregnancy outcomes, delivery, postpartum, and breastfeeding in the context of IBD and IBD medications. Adult IBD patients were invited to participate in the study by accessing the modules and completing questionnaires before, after, and six months after access. Participants were asked IBD-specific questions about 7 pregnancy and 9 medication concerns. McNemar's and Wilcoxon non-parametric tests determined if participants' concerns improved post-intervention and endured six months later. Statistical analysis used SPSS 23.0 with $P<0.05$.

RESULTS

Of the 111 patients who registered, 78 (70.3%) completed pre and post-study questionnaires. Demographics: median age 29.3 years (IQR 25.6 - 32.9); 69.2% Crohn's disease; 26.9% ulcerative colitis; 80.3% females, 7.9% currently pregnant and 30.2% previously pregnant. The intervention significantly reduced the proportion of patients who reported IBD-specific reproductive concerns regarding fertility, child-raising stress, birth defects, disease flaring, and breastfeeding. Medication concerns regarding anxiety, dependency, and long-term effects were also significantly reduced post intervention. Of the 78 patients, 38 (47.4%) completed six month questionnaires; reproductive concerns remaining statistically reduced.

CONCLUSIONS

The educational web portal immediately reduced the proportion of patients who reported certain concerns about pregnancy in IBD, in addition to concerns regarding their IBD medications. At six months, the majority of reproductive concerns remained lowered. Overall, the web portal is a beneficial resource for IBD patients.

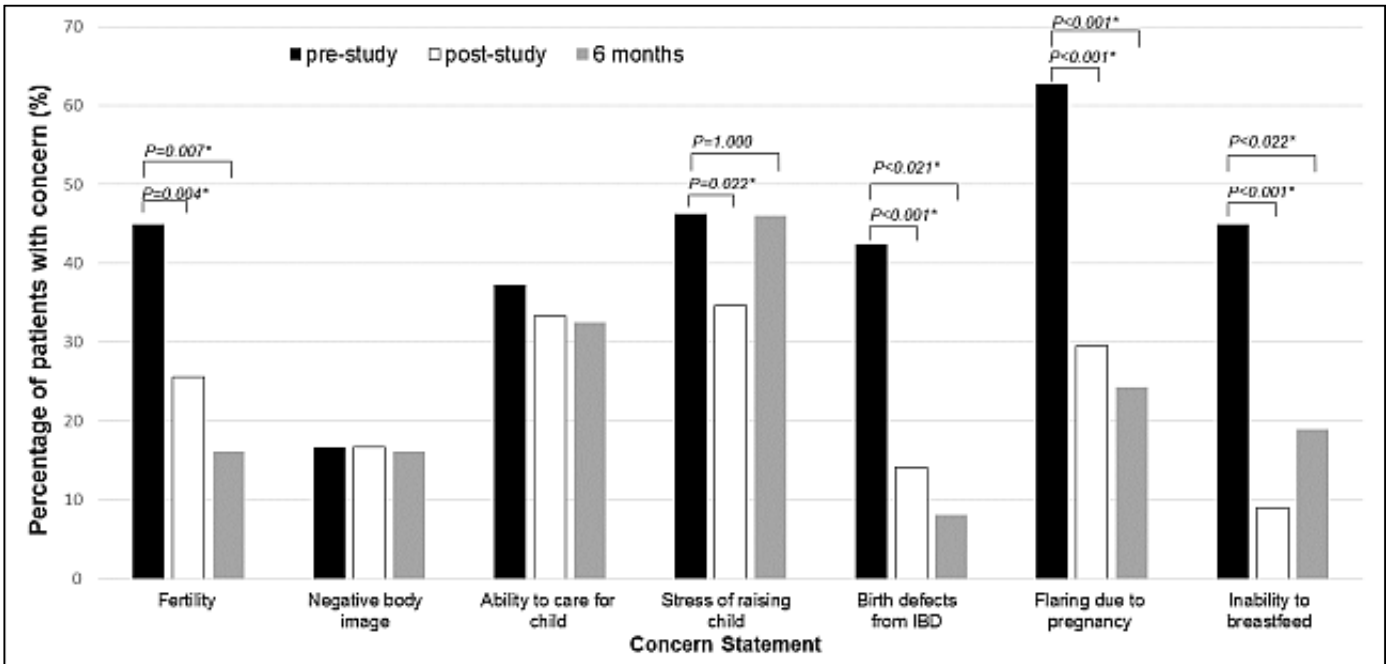

FIGURE 1. IBD-specific reproductive concerns resolve after accessing the web portal. Percentage of patients selecting 'yes" to each concern at pre-study, post-study (n=78), and 6 months (n=37). Statistical significance indicated at P<0.05* (McNemar test).

Characterization of a Novel Metabolic Phenotype in Primary Biliary Cholangitis' Patients' Biliary Epithelial Cells

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INTRODUCTION

Primary Biliary Cholangitis (PBC) is a complex hepatobiliary disorder characterized by loss of bile ducts. It is an autoimmune disease because patients make anti-mitochondrial antibodies (AMA) and autoreactive T-cells targeting the E2 subunit of pyruvate dehydrogenase complex (PDC-E2), a key regulator of glucose oxidation. The AMA strongly react to a protein resembling PDC-E2 on the surface of bile ducts in PBC patients; it is unknown whether this disease specific “mitochondrial phenotype” represents excess production of PDC-E2. Therefore, we assessed mitochondrial and metabolic function in cholangiocytes from PBC patients and relevant controls.

METHODS

Biliary epithelial cells (BEC) were isolated from liver transplant recipients’ livers using immunomagnetic cell separation. Shotgun-proteomics was performed on cholangiocyte lysates. Confirmation of glycolytic activity was performed using isotopic glucose tracing with NMR spectroscopy and western blot of glycolytic enzymes. Mitochondrial respiration was measured using an oxygen biosensor plate and Seahorse XF24. Mitochondrial density was assessed by quantitative PCR (qPCR) for DNA (mtDNA) copy number.

RESULTS

STRING analysis revealed enrichment in protein candidates related to glycolysis. Increased expression of the glycolytic enzyme, ENO2, was validated with western blot ($p<0.05$). NMR of cells and supernatants showed increases in glucose-derived lactate production in PBC BEC ($p<0.01$), indicating elevated glycolysis. The oxygen biosensor revealed mitochondrial respiration was also elevated in PBC BEC ($p<0.01$) and QPCR showed elevated mtDNA levels in PBC BEC ($p<0.05$) indicating mitochondrial biogenesis. Validation of these changes with Seahorse XF24 showed elevated glycolysis ($p<0.05$) and a trend for increased respiration in PBC BEC.

CONCLUSIONS

These results indicate that PBC BEC have a novel metabolic phenotype with activation of catabolic pathways related to energy production. At this time it is unclear how this may relate to disease pathogenesis; however, given the importance of mitochondrial function in regulating cellular viability and local inflammation, further characterization may provide insight into the development of PBC.

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Written patient education materials impart knowledge but do not influence behavior change or patient outcomes: A systematic review.

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INTRODUCTION

Written materials are an important component in imparting the knowledge, skills, and attitudes (KSAs) that Home Hemodialysis (HHD) patients require to manage their own care. Unfortunately, there is little evidence of the impact of this educational approach, or what characterizes effective materials in the HHD context. We reviewed the literature to determine whether written materials are effective for imparting KSAs to patients, and to identify characteristics of effective materials.

METHODS

We searched literature indexed in MEDLINE, CINAHL, ERIC, and PsychINFO from inception to January 2017, for evaluative studies of written instructional materials designed for any type of patient whose educational needs overlapped those of HHD patients. We included studies which evaluated the impact of a specific written education material on patients' knowledge, health behaviors, and outcomes. We excluded studies which evaluated the quality of information/readability of educational materials. Two reviewers independently abstracted information about the studies' quality, targeted patient group, the materials' educational objective, the type of educational event embodied by the material, and its effectiveness.

RESULTS

Our search yielded 1,660 results; 150 met inclusion criteria. Modal quality of the studies was high, and materials targeted various patient groups. Common educational objectives included counseling patients about their condition/medications to promote adherence, providing information about procedures to reduce anticipatory anxiety, and providing strategies for improving their quality of life. Most materials presented expository information; few engaged patients interactively through questions, tests, journaling, etc. There was some evidence that materials increased patients' knowledge; however, when compared to the extemporaneous, in situ presentation of information by healthcare providers, written materials had no additional effect on patients' KSAs or outcomes.

CONCLUSIONS

Pamphlets, brochures, leaflets, and web sites present patients with pertinent information, but they should not be regarded as educating patients. Presenting information is one component of a more complex and interactive process of constructing knowledge.

Notes