

Research DAY

Department of Medicine 2014

GRADUATE STUDENTS | RESIDENTS | POSTDOCTORAL FELLOWS



THURSDAY, MAY 15, 2014

ORAL PRESENTATIONS

CLASSROOM D

2F1.04 WALTER MACKENZIE CENTRE

POSTER PRESENTATIONS

LOWER LEVEL

JOHN W SCOTT HEALTH SCIENCES LIBRARY



Research DAY

Department of Medicine 2014

Welcome to the Department of Medicine Research Day.

This is one of the most important and rewarding days in our academic year when we hear about the exciting research projects in which our Graduate Students, Post Doctoral Fellows, Core Internal Medicine and Subspecialty Residents are involved.

This year our two guest oral adjudicators are Dr. Jeff Saver, Director of the UCLA Stroke Unit & UCLA Comprehensive Stroke Center and Dr. Sandra Davidge, Director of Research, Department of Obstetrics & Gynecology, University of Alberta.

Research Day gives the opportunity for all Department members and guests to interact with our young researchers. We currently have a total of 63 Graduate Students, 24 Postdoctoral Fellows and 185 Core Internal Medicine and Subspecialty Residents. As such, I would encourage you to attend the oral presentations in Classroom D and visit at least three posters which will be located in the lower level of the John W Scott Library.

Enjoy today and be sure to join us for the presentation of awards at the conclusion of the afternoon oral presentations.”

Barbara J. Ballermann, MD

**Instead of an introduction from Evangelos Michelakis,
Associate Chair (Research), Department of Medicine**

The First Step

The young poet Evmenis
complained one day to Theocritos:
“I have been writing for two years now
and I have composed just one idyll.
It’s my only completed work.
I see, sadly, that the ladder of Poetry
is tall, extremely tall;
and from this first step I now stand on
I will never climb any higher.”
Theocritos replied: “Words like that
are improper, blasphemous.
Just to be on the first step
should make you happy and proud.
To have come this far is no small achievement:
what you have done is a glorious thing.
Even this first step
is a long way above the ordinary world.
To stand on this step
you must be in your own right
a member of the city of ideas.
And it is a hard, unusual thing
to be enrolled as a citizen of that city.
Its councils are full of Legislators
no charlatan can fool.
To have come this far is no small achievement:
what you have done already is a glorious thing.”

Constantine Cavafy
(a Greek poet, ~1926)

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Research Day Guest Oral Adjudicators



Jeffrey Lawrence Saver, MD

Director of the UCLA Stroke and Comprehensive Stroke Center, Medical Director of the UCLA Stroke Unit and Program Director of the UCLA Comprehensive Stroke and Vascular Neurology Program, Dr. Saver earned his medical degree from Harvard Medical School in 1986 and completed his extensive postdoctoral training in 1992 with his fellowship in Cerebrovascular Disease at Brown University. Dr. Saver is internationally recognized for his pioneering clinical research in stroke and was recently recognized by the American Heart Association with the prestigious FEINBERG award. He is a superb

teacher as well and has mentored several of our neurology faculty.

Sandra Davidge, PhD

Dr. Davidge is the Director of the Institute for Women & Children's Health Research. She studies mechanisms for normal cardiovascular adaptations of pregnancy as well as mechanisms for impaired vascular responses in women with pre-eclampsia, a pregnancy disorder characterized by hypertension. She has published hundreds of important papers and is funded by several CIHR grants. Her work is characterized by a strong translational approach.



Panel of Judges

Jeffrey Saver, MD

Professor, Neurology

Director, UCLA Stroke Unit

Director, UCLA Comprehensive Stroke Center

University of California, Los Angeles

Sandra Davidge, PhD

Professor, Department of Obstetrics & Gynecology

Director of the Institute for Women & Children's Health
Research

Division Director, Division of Reproductive Sciences

University of Alberta

Barbara J. Ballermann, MD

Professor of Medicine

Chair, Department of Medicine

Zone Clinical Department Head, Internal Medicine

University of Alberta

Session Chairs

Madsen, Karen, PhD

Graduate Education Coordinator
Division of Gastroenterology
University of Alberta

Darryl Rolfson, MD

Director, Postgraduate Medical Education, Internal Medicine
Division of Geriatric Medicine
University of Alberta

Meeting at a Glance

8:00-8:05	Welcome Address
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8:30-9:45	Oral Presentations
9:45-10:00	Break
10:00-11:00	Oral Presentations
11:00-1:00	Poster Presentations and Lunch
1:00-1:15	Translational Fellowship Award
1:15-2:15	Oral Presentations
2:30-2:45	Break
2:45-4:00	Oral Presentations
4:00	Award Ceremony



Morning Oral Presentations

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9:15	Thaker, Harsh Supervisor: Andrew Mason	GS Mouse Mammary Tumor Virus (MMTV) Associated With Onset Of Spontaneous Colitis In IL-10 Deficient Mice	28
9:30	Mojiri, Anahita Supervisor: Nadia Jahroudi	GS Epigenetic Modification Of An Exclusive Endothelial Cell Gene, Von Willebrand Factor (VWF) Activates Its Transcription In Some Cancer Cells.	29
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Morning Oral Presentations

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Scoring Criteria

Oral & Poster Presentations (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	<hr/> 35

Clinical assessment is not sufficient to evaluate volume status in hemodialysis patients

Sylvia Kalainy, Ryan Reid, Kailash Jindal, Branko Braam
Supervisor: Branko Braam

INTRODUCTION

Determining the dry weight of haemodialysis (HD) patients remains a challenge. Yet, hypervolemia is associated with hypertension, heart failure and mortality. Therefore, it remains important to search for clinical parameters that can predict hypervolemia in a HD patient. Using Bio-impedance to assess fluid volume, we hypothesized that a combination of clinical parameters could be used to predict volume status in HD patients.

METHODS

Multifrequency Bio-impedance spectroscopy (BCM- Fresenius Canada) measurement was performed before the start of a mid-week dialysis session in 90 HD patients to assess extracellular fluid volume (ECFV) and hydration status (HS). Physical signs (blood pressure, edema), plasma Na, K and albumin, urea reduction ratio (URR), and a recent CXR (cor-thorax ratio) were investigated as potential markers for volume overload.

RESULTS

Volume status of 90 HD patients (age 61 (23-86) y, 63% males, 24% diabetic) was divided into 2 groups: normovolemia ($HS < 1.1L$, $n=49$) and hypervolemia ($HS \geq 1.1L$, $n=41$). Blood pressure was significantly higher in hypervolemic patients. When the entire group was evaluated, no significant correlations between continuous variables and HS was detected except for a weak correlation with pre-dialysis SBP. An attempt to combine variable into a "fluid overload score" failed. We also detected a significant number of patients with dehydration.

CONCLUSIONS

Assessment of volume status using clinical parameters only failed to identify patients with volume overload. Antihypertensive medications might obscure clear relationship between BP and OH. Our data indicate a place for more objective method such as Bio-impedance to identify volume overload in HD patients. Our future plan is to correct patients with hypervolemia according to the BCM measurements and follow up for blood pressure and cardiovascular risk in these patients.

Supervisor: Dr. Branko Braam

	Normovolemic	Hypervolemic
Gender, M/F	26/23	31/10*
Age, years	61± 16	62± 13
HS, L	-0.2± 1.01	2.7± 1.4*
HS/ECW, %	-1.3± 6	15± 6*
HS/BW, %	-0.1± 0.17	3.6± 0.2*
Hypertension, % (on BP medications)	40	60*
Diabetes, %	43	53
Smoking, %	6	22
Edema, %	18	56*
Obesity, %	30	20
Pre-HD SBP, mmHg	127± 24	139± 20*
Pre-HD DBP, mmHg	71± 17	76± 15*
Pre-HD MAP, mmHg	89± 17	97± 15*
Pre-HD PP, mmHg	57± 3.09	63± 2.4

*P<0.05

Correlation of ex vivo MRI-based hippocampal subfield volumetry and neuronal cell densities

Steve TA, Coras R, Livy DJ, Malykhin NV, Moez EK, Dinu I, Blumcke I, Gross DW
Supervisor: Dr. Donald W Gross

INTRODUCTION

Hippocampal sclerosis (HS), a common pathologic finding in medically intractable epilepsy, consists of several histological subtypes with diverse surgical prognoses. Hippocampal subfield volumetry, using high-field MRI, has been proposed as a potential technique for diagnosing HS subtypes preoperatively. The use of volumetry for this purpose is based on the hypothesis that a relationship exists between hippocampal subfield volumes and neuronal densities. We therefore aimed to assess the correlation between subfield volumes and densities, using ex vivo MRI of autaptic hippocampus specimens.

METHODS

Autaptic hippocampi were removed post-mortem from six individuals (age 61-96) without history of epilepsy or other neuropsychiatric diseases. Fast spin echo sequences (voxel size 0.02 mm^3) were performed on a 4.7 tesla MRI scanner. Hippocampal subfield volumes were measured at four anatomical sites of each hippocampus ($n=6$), for a total of twenty-four measurements. Following MRI, specimens were paraffin-embedded and sectioned with a microtome. Neuronal densities were measured, at anatomical sites corresponding to those used for volumetry, from histological slides stained with H&E. A mixed effects linear model was used to assess the relationship between hippocampal subfield volumes and neuronal densities; effects of subject age and anatomical location of sampling on neuronal densities were also modelled.

RESULTS

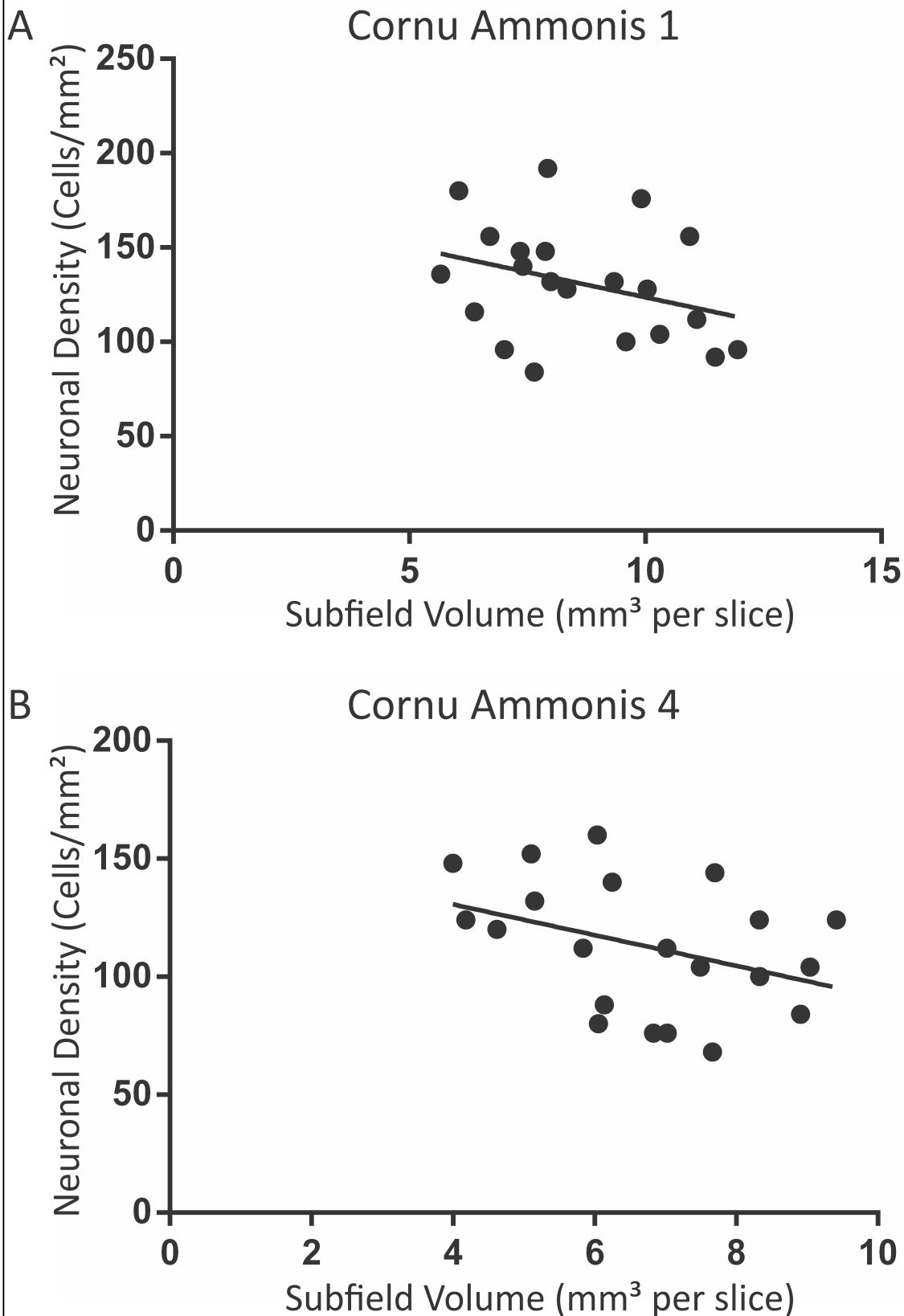
In the CA1 subfield, a statistically significant inverse relationship between sector volume and neuronal densities was demonstrated ($p=0.0083$). A significant inverse relationship between age and CA1 neuronal densities was also seen ($p=0.0203$). Effects of location on cell counts were not statistically significant ($p=0.1591$). Neuronal densities and subfield volumes in CA4 also demonstrated an inverse relationship, but this was not statistically significant ($p=0.0921$). Neither age ($p=0.1520$) nor location ($p=0.8132$) had a significant effect on CA4 neuronal densities.

CONCLUSIONS

Hippocampal subfield volumes correlated inversely with neuronal densities, particularly in the CA1 subfield. Hippocampal subfield volumetry is a promising tool for detection of subfield atrophy patterns in vivo.

Supervisor: Dr. Donald W Gross

Figure 1: Correlation of MRI volumes and neuronal densities



Scatter plots showing correlation between subfield volumes and neuronal densities in hippocampal subfields. A statistically significant ($p=0.0083$) inverse relationship between sector volume and neuronal densities was demonstrated in the CA1 subfield (A). A trend ($p=0.0921$) towards inverse correlation was observed in the CA4 subfield, which was not statistically significant (B).

Hypertensive Kidney Injury in CLIC5A Deficient Mice

Mahtab Tavasoli^{1*}, Laiji Li¹, Lin-fu Zhu², Benjamin Alexander Adam¹ and Barbara J. Ballermann¹
Supervisor: Dr. Barbara Ballermann

INTRODUCTION

The exterior surface of renal glomerular capillaries is wrapped by finger-like podocyte foot processes which create a large surface area for selective filtration of water and small solutes, and provide capillary wall strength in the face of the high (~ 50 mmHg) glomerular capillary pressure. CLIC5A, highly enriched in podocytes, is a scaffolding protein that regulates PI[4,5]P₂ production in apical plasma membrane patches, promoting ezrin docking, phosphorylation and actin coupling, which maintain the unique podocyte architecture. Here, we hypothesized that CLIC5A is required to protect glomerular capillaries from hypertension-induced injury.

METHODS

Uninephrectomized CLIC5A deficient (CLIC5A^{-/-}) and wild-type (CLIC5A^{+/+}) mice were treated with deoxycorticosterone and 1% saline drinking water (DOCA/Salt). Blood pressure (BP), urinary albumin:creatinine ratio (ACR) and renal histology were evaluated 20 days after DOCA/Salt initiation. Foot process and endothelial fenestrae density were quantified by morphometry/transmission electron microscopy.

RESULTS

DOCA/Salt raised the systolic BP similarly in CLIC5A^{+/+} and CLIC5A^{-/-} mice. However, urinary albumin, microaneurysm formation, foot process effacement and loss of glomerular fenestrae were greater in CLIC5A^{-/-} compared to CLIC5A^{+/+} mice (Table 1).

CONCLUSIONS

Thus, glomerular hypertensive injury is greater in CLIC5A^{-/-} than CLIC5A^{+/+} mice, consistent with the hypothesis that CLIC5A provides capillary strength.

Supervisor: Dr. Barbara Ballermann

Table 1. Comparison of CLIC5A^{+/+} and CLIC5A^{-/-} mice treated with DOCA/Salt

	CLIC5A ^{+/+}	CLIC5A ^{-/-}
Systolic BP (mm Hg; baseline / day 20)	98 ± 8 / 119 ± 6	97 ± 8 / 121 ± 11
Urinary Albumin (ACR, mg/g)	780 ± 235	1,720 ± 960*
% of glomeruli with microaneurysms	31 ± 17	57 ± 18*
Foot Processes per μm GBM	2.55 ± 0.10	1.91 ± 0.09**
Endothelial Fenestrae per μm GBM	2.63 ± 0.35	1.25 ± 0.20**

(Mean ± SEM, n=5/group, *p < 0.05; **p < 0.01)

Mouse mammary tumor virus (MMTV) associated with onset of spontaneous colitis in IL-10 deficient mice

Thaker HR, Hotte N, McDougall C, Reuter B, Thiesen A, Madsen KL, Mason AL
Supervisor: Dr. Andrew Mason

INTRODUCTION

Inflammatory bowel disease (IBD) is increasing in prevalence in developed countries with a limited understanding of the underlying cause. Our laboratory is interested in studying IBD and has used an IL-10^{-/-} mouse model with spontaneous colitis. We observed high levels of Mouse mammary tumor virus (MMTV) in this model when samples were used as a control in unrelated experiments. Recent reports have shown that MMTV infection induced tolerance when taken up into the gastrointestinal tract by triggering the secretion of IL-10, which is an anti-inflammatory cytokine. We observed that IL-10^{-/-} mice had increased levels of MMTV in the small bowel, colon and liver as compared to wild type (WT) mice. In order to address the hypothesis that MMTV infection was related to IBD in the IL-10^{-/-} colitis model, we investigated whether the phenotype could be improved by treating with anti-retroviral therapy.

METHODS

IL-10^{-/-} and WT mice were treated with Truvada and Kaletra therapy or placebo in drinking water for 10 weeks and sacrificed at 18 weeks of age. MMTV RNA was measured using quantitative RT-PCR and QuantiGene. Intestinal inflammation was scored by histology. Immune function was measured via ELISA using the MesoScale platform for pro-inflammatory cytokines.

RESULTS

IL-10^{-/-} mice treated with antiviral therapy had a reduction in viral load which correlates with a decrease in overall histological score compared to IL-10^{-/-} on placebo. Pro-inflammatory cytokines (IL-1 β , IFN γ , TNF α) were increased in the small intestine and colon of IL-10^{-/-} mice relative to WT and the anti-retroviral therapy reversed the trend.

CONCLUSIONS

MMTV levels in IL-10^{-/-} mice are higher than in WT mice due to an inability to clear the infection. Viral load can be reduced by antiviral therapy and is correlated with reduced intestinal inflammation. Our data suggest that MMTV may be partially responsible in generating the IBD phenotype observed in the IL-10^{-/-} mice.

Supervisor: Dr. Andrew Mason

Epigenetic modification of an exclusive endothelial cell gene, Von Willebrand Factor (VWF) activates its transcription in some cancer cells.

Anahita Mojiri, Nadia Jahroudi
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

VWF is an adhesive procoagulant molecule that is specifically expressed in endothelial cell (EC). VWF mediates adhesion of platelets to the damaged EC surfaces. Both increased plasma levels of VWF, and increased thrombosis in cancer patients are reported. The importance of VWF as an adhesive and prothrombic molecule, suggests it may have a potential role in cancer metastasis. We hypothesised that epigenetic modification of VWF gene leads to expression of VWF in some cancer cells.

METHODS

Several glioma, osteosarcoma, and breast cancer cell lines were analysed for expression of VWF mRNA and protein. The binding patterns of VWF transacting factors and histone modifications on the VWF chromatin were analyzed by chromatin Immuno-precipitation (ChIP) assays. In vitro cell-cell interaction, comparable to physiological conditions, was used to demonstrate the effect of VWF expression in cancer cells adhesion to platelet and EC surfaces.

RESULTS

RT-PCR, western blot analyses and immune-fluorescent staining showed significant levels of VWF expression in gliomas (U251, M016, M049), some breast cancer, and osteosarcoma Saso2 cell lines, but not in other comparable cancer cells (i.e Osteosarcoma-KHOS). ChIP assays demonstrated that transcription factors (repressors-activators) bind to the VWF promoter in these cancer cells in a similar pattern as was observed in EC. The epigenetic modification analysis showed that histone modification of the VWF promoter in gliomas (U251, M016, M049) and Saso2 is consistent with transcriptional activation of the VWF promoter in these cells. In vitro cell-cell interaction showed that cancer cell lines expressing VWF, exhibit increased adhesion to the platelet and endothelial monolayer under the shear stress.

CONCLUSIONS

De novo expression of VWF in cancer cells is a unique feature that occurs as a result of epigenetic modification of the VWF promoter and associated transacting factors. Acquired VWF expression by cancer cells could contribute to their metastatic potential.

Supervisor: Dr. Nadia Jahroudi

Chronic brain administration of amylin receptor antagonist, AC253, attenuates spatial memory and learning deficits in A β over-expressing (TgCRND8) mice

Patel AN, MacTavish D, Yang J, Westaway, D and Jhamandas JH
Supervisor: Dr Jack Jhamandas

INTRODUCTION

Alzheimer's disease (AD) is characterized by accumulation of amyloid- β peptide (A β) in the brain regions that subserve memory and cognition. We have previously demonstrated that electrophysiological and neurotoxic effects of A β can be blocked by the amylin receptor antagonist, AC253. In this study, we examined the ability of chronic intracerebroventricular (icv) infusions of AC253 to restore spatial memory deficits in transgenic mice that over-express A β (TgCRND8).

METHODS

Wild-type (Wt) or TgCRND8 mice (3 months old) received implants of cannulae connected to Alzet osmotic mini-pump for chronic icv delivery of either ACSF or AC253 (0.91 μ g/ μ l) for 10 months. Hippocampal-dependent spatial learning and memory was assessed in a standard Morris water maze (MWM) or using a simple food rewarded discrimination task with a T-maze apparatus.

RESULTS

The acquisition phase (escape latency) in MWM task, TgCRND8 mice had significantly longer escape latencies over the 7-day testing period than their respective Wt littermate controls at 4, 6, 8, 10 and 12 months of age. However, TgCRND8 mice continuously infused with AC253 showed significantly shorter escape latencies in MWM at later time points (i.e. at 8, 10 and 12 months of age) compared to TgCRND8 treated with ACSF alone. During the MWM probe test, AC253 treated TgCRND8 mice increased the number of platform crossings and also the amount of time spent in the target quadrant (location of the platform during the final session of the MWM acquisition phase) compared to TgCRND8 treated with ACSF alone. Similar results were observed in food rewarded T-maze alternation task, where AC253 treated TgCRND8 mice showed reduced errors in alternation tasks compared to TgCRND8 treated with ACSF alone.

CONCLUSIONS

These studies provide first in vivo evidence for the utility of amylin receptor antagonist, AC253, in mitigating spatial memory learning deficits in a mouse model of AD.

Supervisor: Dr Jack Jhamandas

In IBD outpatients knowledge of fecal calprotectin and infliximab trough levels significantly alters clinical decision making

Huang, V; Prosser, C; Shalapay, C; Kroeker, KI; Wang, Haili; Dhami, Neil; Fedorak, Darryl K; Dieleman L; Fedorak, Richard N

Supervisor: Dr. Richard Fedorak

INTRODUCTION

Infliximab (IFX) is an effective, but costly, therapy for inflammatory bowel disease (IBD). It is dosed by weight (5mg/kg) and administered every 8 weeks during maintenance. Over 50% of patients will lose response within 3 ys, resulting in IFX dose intensification. Most often the decision for dose intensification is made on clinical assessment. Nevertheless, one third of patients with symptoms do not have actual disease recurrence. The aim of this study was to determine if objective measures of inflammation using fecal calprotectin (FCP), and infliximab trough levels (ITL) would lead to different management decisions of patients on infliximab than those made when only clinical assessment was available.

METHODS

IBD patients receiving IFX were consented to provide stool and blood samples prior to their infusion and to complete clinical activity scores. Stool FCP and blood ITL were analyzed by immunodiagnostic ELISA. Three decisions were then compared: (1) Actual clinical decision (ACD): made by the IBD clinician blinded to FCP/ITL (2) FCP/ITL algorithm decision: FCP > 250 µg/g led to an action, ITL <3.0 or > 7.0 mg/mL led to an action (3) Expert consensus decision (ECD): made by 3 IBD clinicians given clinical data and FCP/ITL. Decisions could be: no change v. action (Investigate, dose change, switch drugs).

RESULTS

The FCP algorithm decision was different from the ACD in 46.2% of cases. The ITL algorithm decision was different from the ACD in 74.4% of cases. The addition of FCP to ECD triggered investigation in 28.2% additional cases. The addition of ITL to ECD plus FCP decision triggered IFX dose escalation in 7.7% additional cases, and IFX dose de-escalation in 20.5% additional cases, and avoided investigations in 7.7% cases.

CONCLUSIONS

The addition of objective measures of FCP and/or ITL to clinical decisions regarding infliximab dosing may be useful but requires further study.

Supervisor: Dr. Richard Fedorak

Are older women more likely to receive less invasive surgical options for stress urinary incontinence since the introduction of the mid-urethral sling?

William Gibson, Adrian Wagg
Supervisor: Dr Adrian Wagg

INTRODUCTION

Many surgical treatments have been developed for the treatment of stress urinary incontinence (SUI). Since the introduction of the mid-urethral sling (MUS) in 1996 there has been a rapid reduction in the number of colposuspensions performed. MUS is safe and effective in older as younger women, and given that less invasive procedures require a shorter stay in hospital, and can be performed under local anaesthesia, it may be anticipated that older women who have been shown to benefit from these less invasive surgical procedures would make up a greater proportion of patients receiving them. This study tested the hypothesis that there would be an increase in the proportion of MUS performed in older women over time.

METHODS

UK Hospital Episode Statistics from 2000 -2012 were examined for a change in the age distribution of women receiving MUS, urethral bulking agents and open procedures for SUI. Using the procedure specific 4-digit code, we calculated the number of invasive procedures, MUS, and injection of bulking agents (UBA) performed in women by age category 15-59, 60-74, and 75+.

RESULTS

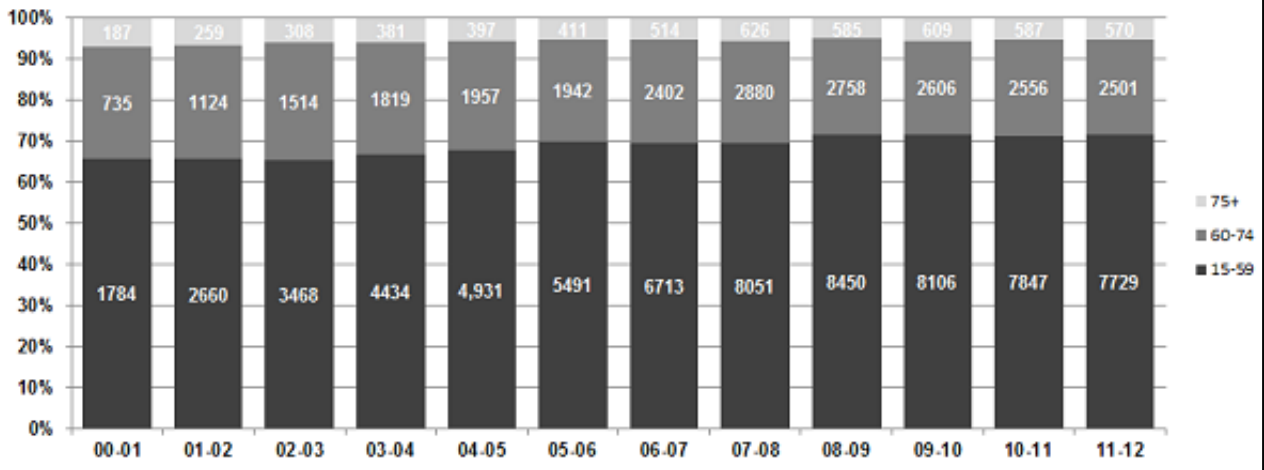
127,469 Finished Consultant Episodes were recorded. The number of more invasive procedures declined over time. There was no change in the proportion of older women receiving MUS or UBA. Older women made up a greater portion of those receiving UBA. (Figure 1)

CONCLUSIONS

Despite an aging population, an increase in the absolute number of women with SUI and the development of safe and effective surgical treatments for SUI with lower potential for adverse events, the proportion of older women undergoing surgery for SUI has not risen over the last ten years. The reasons for this are unknown

Supervisor: Dr Adrian Wagg

Mid-Urethral Slings by Age Group



Fingerprinting of the Plasma Renin-Angiotensin-System Peptides in Chronic Heart Failure Patients: Insights into Personalized Therapy for Heart Failure

Ratnadeep Basu^{1, 2}, Marko Poglitsch³, Jissy Thomas² and Gavin Y. Oudit^{1, 2}
Supervisor: Gavin Y. Oudit

INTRODUCTION

Heart failure (HF) patients represent a vulnerable patient population with unacceptably high morbidity and mortality. Activation of the renin-angiotensin system (RAS) plays a key pathophysiological role in HF. Indeed, a mainstay of current pharmacological treatment is the use of angiotensin converting enzyme I inhibitors (ACEI). However, angiotensin II is just one among several other peptides formed during the proteolytic degradation of the parent peptide angiotensin I (1-10).

METHODS

We screened 22 chronic HF (CHF) patients (ambulatory and receiving ACE inhibitors and beta blockers) compared to 12 healthy controls (age and gender matched) for the quantification of sequential cleaved products of Angiotensin I (Ang 1-10). Adequate quantification of the circulating angiotensin peptide levels (in-vivo) was achieved after stabilizing these degradation sensitive peptides. Plasma was harvested and stored at -80°C and subjected to 10 different angiotensin peptide quantification using a novel liquid chromatography-mass spectrometry (LC-MS/MS)-based approach.

RESULTS

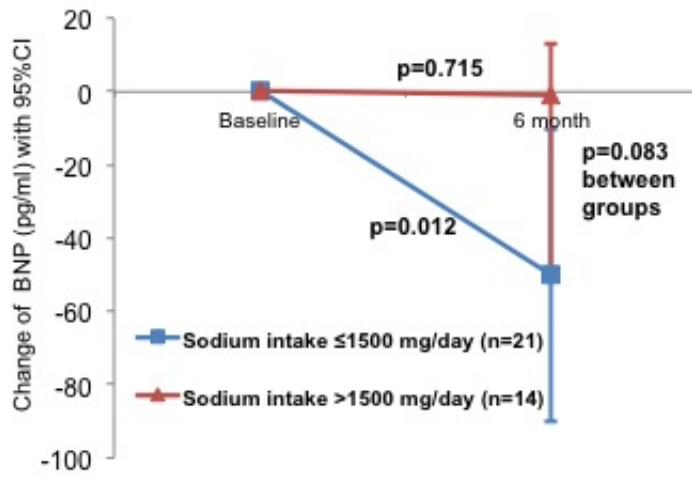
RAS fingerprint acquired from CHF patients compared to healthy controls (HC) revealed significant decrease in Ang II (1-8) levels (CHF: 4.18 ± 0.7 pg/ml vs. HC: 7.06 ± 1.60 pg/ml; $p < 0.05$). This correlated to a simultaneous increase in the levels of circulating Ang I (1-10) in the CHF group (270 ± 51 vs. 12.9 ± 3.3 ; $p < 0.01$). Interesting, the circulating levels of Ang 1-7 in CHF compared to the HC group (9.55 ± 1.89 vs. 2.15 ± 0.15 ; $p < 0.05$) were increased without any change in the levels of other circulating peptides such as Ang III (2-8), Ang IV (3-8) and Ang 1-9.

CONCLUSIONS

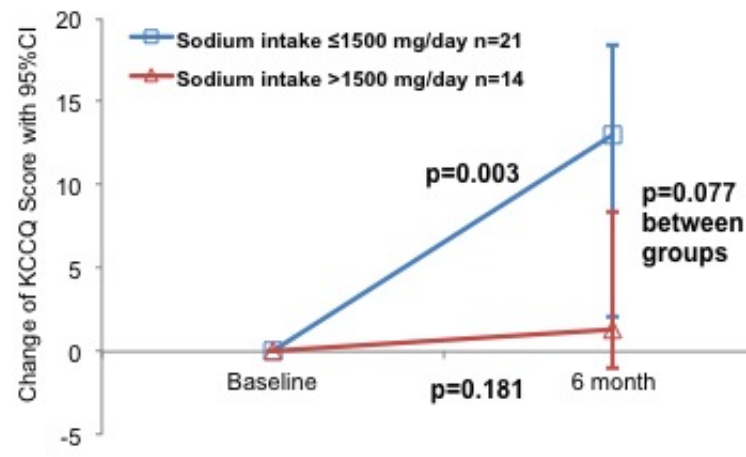
The compensated clinical stability of CHF patients treated with ACEI is associated with a combined effect of decreasing plasma Ang II levels as well as increasing Ang 1-7 levels. Ang 1-7 is well known to be protective in the cardiovascular system and elevated Ang 1-7 levels may contribute towards the beneficial effects of ACE inhibitors.

Supervisor: Dr. Gavin Y. Oudit

(a) BNP



(b) KCCQ



Adalimumab dose escalation is effective for secondary loss of response in outpatients with inflammatory bowel disease

Christopher Ma, Vivian Huang, Darryl K. Fedorak, Karen I. Kroeker, Levinus A. Dieleman, Brendan P. Halloran, and Richard N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Adalimumab, a monoclonal antibody against tumour necrosis factor alpha has been shown to be effective in induction and maintenance of response in IBD patients. However, a subset of patients will experience secondary loss of response which can be overcome with dose escalation. Long-term outcomes after adalimumab dose escalation in this population have not been well evaluated.

METHODS

A retrospective cohort study evaluating outpatients with Crohn's disease (CD) or ulcerative colitis (UC) requiring adalimumab dose escalation from 2004-2013 was conducted. Patients with ileostomy or pouch were excluded. Clinical response was defined by improvement in clinical disease activity indices (Harvey-Bradshaw Index, partial Mayo score), endoscopic healing, or physician global assessment within 24 weeks of escalation. Kaplan-Meier analysis was used to determine duration of sustained response after escalation and multivariate logistic regression was used to identify predictors for loss of response.

RESULTS

116 patients (90 CD, 26 UC) met inclusion criteria. Disease distribution was predominantly ileal (41.1%) or ileocolonic (45.6%) for CD; 76.9% of UC patients had pancolitis. Median partial Mayo score at induction was 6.0 (IQR 4.0-8.0); median HBI at induction was 9.0 (7.0-12.0). Mean duration of follow-up was 172.2 weeks (CD) and 143.7 weeks (UC).

87.8% (79/90) of CD and 76.9% (20/26) of UC patients responded to adalimumab dose escalation. Subsequent loss of response occurred in 42/79 (53.2%) CD and 6/20 (30.0%) UC patients at a mean time of 67.4 weeks and 22.8 weeks, respectively. CRP > 10mg/L at escalation was associated with increased risk of loss of response (OR 5.01, 95%CI: 1.39-18.04) and previous anti-TNF exposure was associated with earlier loss of response (Figure 1) in CD patients.

CONCLUSIONS

Over 75% of IBD patients regain clinical response with adalimumab dose escalation but this is sustained only in a subset of patients. Previous anti-TNF exposure and high CRP at escalation increase the risk of relapse.

Supervisor: Dr. Richard Fedorak

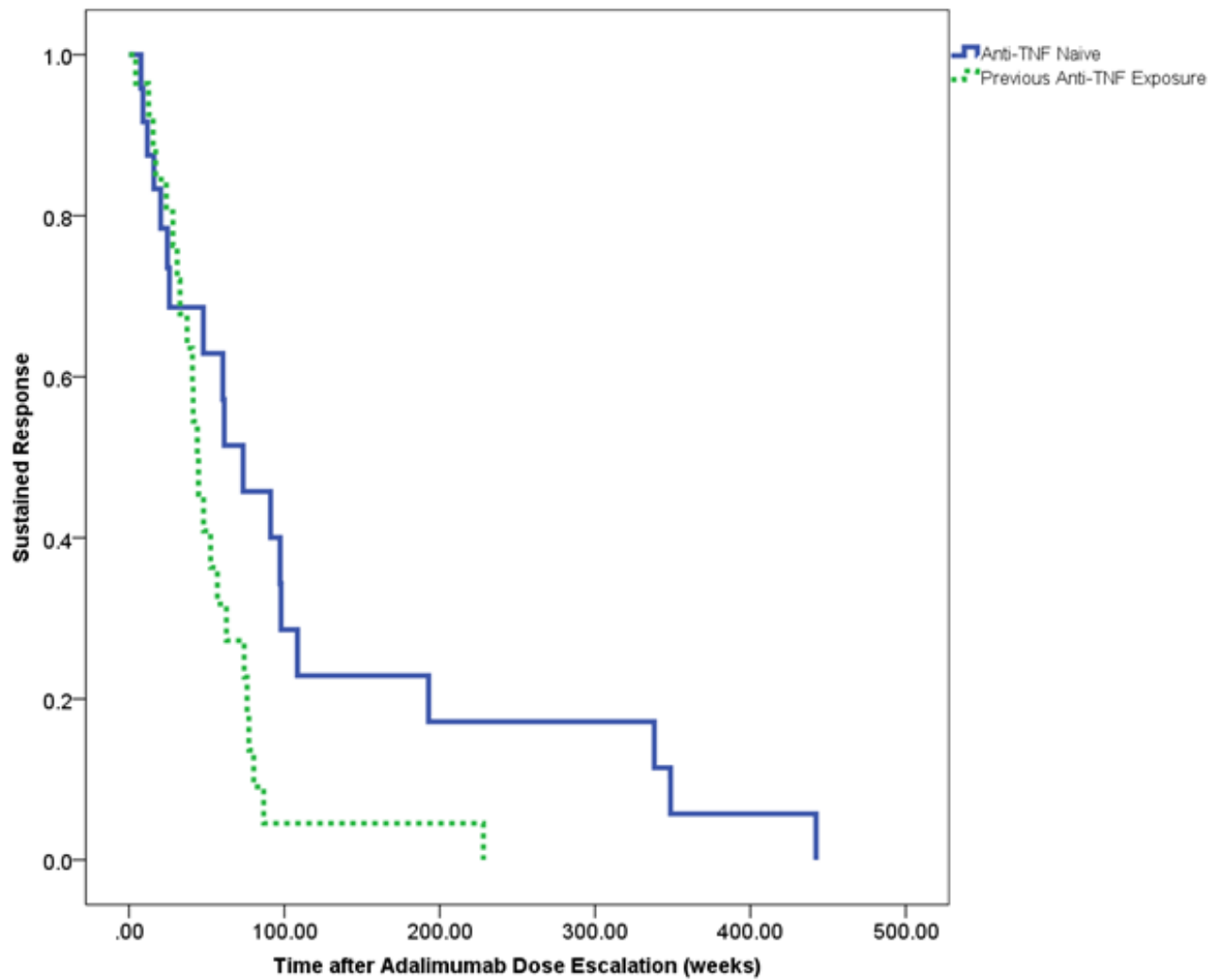


Figure 1 – Kaplan-Meier survival curves of maintenance of clinical response after dose escalation of adalimumab for CD patients with previous anti-TNF exposure (green hashed) vs. anti-TNF naïve (blue solid). $p = 0.038$.

Enhanced Tuberculosis (TB) Screening Program for Refugees in Edmonton, Canada: High-Completion Rates Facilitated by Prompt Referral and Assessment Upon Arrival

Elissa Rennert-May, MD (1), Elisabeth Hansen, RN (3), Stan Houston, MD (1,2), Toktam Zadeh, BScN (3), Ryan Cooper, MD, MPH (1,2,3)

Supervisor: Dr. Ryan Cooper

INTRODUCTION

Over half of new Tuberculosis (TB) cases in North America each year occur in foreign-born individuals. Refugee populations are considered at particularly high risk in the first few years after immigration. In Edmonton, all government-sponsored refugees receive prompt medical evaluation at the New Canadians' Clinic within a few weeks of arrival to Canada.

METHODS

We retrospectively reviewed consecutive patients at the Edmonton New Canadians' Clinic TB screening program evaluated between 2009 and 2011. We sought insight into completeness of initial assessment, diagnosis of latent infection, and adherence to TB prophylaxis.

RESULTS

During the three-year interval, 949 refugees were evaluated. All (100%) received an initial assessment by a TB nurse with subsequent chest x-ray (CXR) and tuberculin skin test (TST) if required. 746 TSTs were successfully planted and read, of these, 265 (36%) were positive. Confirmation with Interferon-Gamma Release Assay (IGRA) testing was performed in 203 TST positive individuals without other TB disease risk factors. Of the IGRAs performed, 54% were positive, suggesting a high "false-positive" TST rate, even amongst these highly selected patients. Sub-Saharan Africans were more likely to have IGRA confirmation than refugees from other regions (75/105 (71%) versus 35/93 (38%) $p < 0.005$).

Of the 949 refugees, self-administered TB prophylaxis was offered to 147. Initial acceptance rate was very high with 141 (96%) taking at least one dose of prophylaxis and 103 (73%) completing an entire course of TB prophylaxis. Statistically significant correlates of non-adherence to therapy include young age ($p=0.039$) and Sub-Saharan African origin ($p<0.005$). Only 64% of Sub-Saharan African refugees completed TB prophylaxis.

CONCLUSIONS

In summary, we observed a very high degree of patient retention with initial TB clinic visits and for completion of TB investigations. Latent TB treatment completion rates were high compared to published results from other programs. This care model promises to be a component of effective TB prevention in refugee populations.

Supervisor: Dr. Ryan Cooper

Epidemiology of Post-Transplant Lymphoproliferative Disorder Following Solid Organ Transplant in a Major Canadian Transplant Centre

Anthea C Peters, MD, M.Sc., FRCPC; Marco Iafolla, MD, M.Sc.; Segun M Akinwumi, MSc; Curtis Mabilangan, BSc; Karen Doucette, MD, M.Sc.; and Jutta Preiksaitis, MD, FRCPC

Supervisor: Dr Anthea Peters

INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are a complication of immunosuppression in solid organ transplantation (SOT) that range from lymphoid hyperplasia to aggressive lymphoma. We describe the epidemiology of PTLD in all SOT patients in a major Canadian transplant centre over an extended time period with complete virology and histology data.

METHODS

We included all patients who received a SOT at the University of Alberta from January 1st, 1984 to December 31st, 2013 for analysis. PTLD diagnoses ranged from early lesions / polymorphic, monomorphic B cell, monomorphic T cell, or Hodgkin lymphoma. Cumulative incidence rate was calculated by % person-year incidence. Risk factors were analyzed by univariate analysis using Cox regression analyses. Time to PTLD was analyzed by binary logistic regression. Survival statistics were calculated using the Kaplan-Meier survival method.

RESULTS

149 of 4952 transplant patients analyzed developed PTLD. Cumulative incidence at 1 year, 5 years, 10 years and 20 years was 4.4%, 9.3%, 10.2%, and 11.4% for pediatrics respectively, and 1.0%, 1.7%, 2.5%, and 3.5% for adults, respectively. Organ transplants with highest incidence rate were heart in pediatrics and multivisceral or small bowel in adults. PTLD significantly worsened overall survival (OS) in the adults ($p = 0.000$) but not in the pediatric patients ($p = 0.32$). Variables that significantly correlated with risk of PTLD in pediatrics included time from transplant, age of patient at transplant, organ transplanted and recipient EBV negative serology. Significant risk factors in adults included time from transplant, organ type transplanted and recipient EBV or CMV negative serology.

CONCLUSIONS

1. New cases of PTLD continued to occur over 20 years post-transplant; the highest incidence rate was in the first year.
2. PTLD had a significant impact on the OS of our adult, but not pediatric, patients.
3. Negative EBV serostatus significantly increased the risk of both early and late PTLD development.

Supervisor: Dr Anthea Peters

Type II MI in Southern Alberta: a descriptive analysis

Deirdre O'Neill MD, Danielle A. Southern MSc, Colleen M. Norris PhD, Blair J O'Neill MD, Michelle M Graham MD
Supervisor: Dr. Michelle Graham

INTRODUCTION

The concept of type II myocardial infarction (MI), or myocardial ischemia due to supply-demand mismatch, was introduced in 2007, causing contention and confusion for many clinicians. We aimed to gather data on a large, unselected population of patients with type II MI and to evaluate investigation, management and prognosis.

METHODS

All patients with a positive troponin over a 2-year period in the Calgary Health Region were identified. Chart review was performed and patients with explicit ACS diagnoses excluded, leaving only patients with troponin elevations presumably associated with type II MI. Follow up data were obtained through the use of the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database and its linkage to the Alberta Bureau of Vital Statistics.

RESULTS

From January 1, 2007 to December 31, 2008, 998 patients with a presumptive diagnosis of Type II MI were identified, with the majority admitted to general practice or internal medicine. Despite the troponin elevation, ECG was not performed in 6%, and one third did not have subsequent ECGs. ECG changes are outlined in Table 1. Echocardiograms were performed in 23.2%, CT PE in 6.2%, and nuclear myocardial perfusion imaging in 0.05%. No patient underwent cardiac catheterization. Outcomes were poor, with in-hospital mortality of 15.2%. For those patients who survived, 30-day mortality was 3.9% and one-year mortality 13.6%, with readmission rates being 13.5% and 35.3% at 30 days and one year, respectively.

CONCLUSIONS

In this large unselected cohort of patients with presumptive diagnoses of type II MI, ECG changes were common, and investigations to rule out type I MI or underlying ischemia were uncommon, raising the possibility of misdiagnosis. Outcomes were poor and readmission rates high, indicating that further research is required to determine appropriate management of this important group of patients.

Supervisor: Dr. Michelle Graham

ECG finding	N (%)
No ECG performed	57 (5.7%)
Dynamic changes compared to baseline	212 (21.2%)
ST segment elevation	52 (5.2%)
ST segment depression	134 (13.4%)
T wave changes	212 (21.2%)
Bundle branch block	154 (15.4%)
Paced ventricular rhythm	18 (1.8%)
No follow up ECG	291 (29.1%)

Comparison of ERCP Outcomes Between Low Volume and High Volume Endoscopists at a Canadian Tertiary Care Centre

Victor Dong, Richa Chibbar, Pernilla D'Souza, Gurpal Sandha, Sergio Zepeda-Gomez, Sander Veldhuyzen van Zanten, Christopher Teshima, Richard Sultanian

Supervisor: Dr. Richard Sultanian

INTRODUCTION

ERCP is a common intervention used to diagnose and treat a variety of hepatobiliary and pancreatic conditions. Despite advances, ERCP can still be associated with significant morbidities like bleeding or pancreatitis. Thus, quality assessment in ERCP is an emerging area of clinical outcomes research. The aim of this project is to study the impact of endoscopist case volume on ERCP outcomes in terms of procedural success and complication rates.

METHODS

A retrospective chart review was done on all ERCPs completed between January 1, 2011 and December 31, 2012. Patient data and case metrics were stratified into two groups based on endoscopist case volumes; high volume ERCP (HVE) defined as at least 75 cases/endoscopist/year and low volume ERCP (LVE) defined as less than 75 cases/endoscopist/year. The groups were compared regarding procedural success and complications.

RESULTS

Six endoscopists (3 HVE and 3 LVE) performed 898 ERCPs during this period; 658 by the HVE group and 240 by the LVE group. Patient demographics were similar in both groups. Overall procedural success rate was 84% versus 69% in the HVE and LVE groups respectively ($p < 0.0001$, OR 2.27). Successful cannulation occurred in 90% of cases in the HVE group versus 82% in the LVE group ($p = 0.002$, OR 1.96). Overall complication rate was 7.3% versus 12% in the HVE and LVE groups respectively ($p = 0.02$, OR 0.57). Post-ERCP pancreatitis (PEP) occurred in 5.3% of cases versus 7.9% in the HVE and LVE groups respectively ($p = 0.15$, OR 0.65) despite the overall complexity score for the LVE group being lower (1.81) than the HVE group (2.07).

CONCLUSIONS

This study demonstrates a significant difference in overall procedural success and complication rates of ERCP favoring high case volumes. This data represents two years of ERCP volume at our centre. Expanding to additional years may provide more insight into how case volume affects patient outcomes.

Supervisor: Dr. Richard Sultanian

Clinical characteristics are not significant predictors of advanced obstructive sleep apnea in the severely obese

Luc Benoit, Atul Malhotra, Calypse B. Agborsangaya, Mohit Bhutani, Justin Sebastian, Raj Padwal
Supervisor: Dr. Raj Padwal

INTRODUCTION

Obstructive sleep apnea (OSA) is a major cause of impaired quality of life and a major risk factor for cardiovascular disease and post-operative complications. OSA is present in 70-93% of severely obese patients receiving bariatric (obesity) treatment. Polysomnography, the gold standard for OSA diagnosis, is not widely available and can be costly to perform. Identifying clinical predictors of moderate-to-severe OSA in the severely obese would enable providers to identify and refer for polysomnography those with a higher likelihood of advanced OSA.

METHODS

A cross-sectional study was performed in patients referred to a pulmonologist for OSA evaluation from a publicly funded, population representative bariatric care program (Edmonton Weight Wise). Patients were referred because of clinical suspicion for OSA. All patients underwent Level 1 or 3 sleep studies. Data elements were collected via electronic medical record abstraction. Moderate-to-severe OSA was defined as an apnea-hypopnea index (AHI). From a list of clinically important potential covariates, multivariable binary logistic regression was used to identify statistically significant predictors ($p < 0.05$) of moderate-to-severe OSA.

RESULTS

Of 169 patients undergoing polysomnography, 161 (95.3%) had complete data. Mean age was 48.8 ± 9.1 , 47 (28%) were male, mean body mass index (BMI) as 49.4 ± 9.7 kg/m², 56% were hypertensive, 33% had diabetes and 28% had depression. 100 (59%) patients had moderate-to-severe OSA and the mean AHI was 27.0 ± 27.3 .

No statistically significant predictors of moderate- to- severe OSA were identified (Table 1). The strongest predictors of OSA were neck circumference (OR 1.08; 95% CI 0.99 - 1.18) and hypertension (OR 1.95, 95% CI 0.92 - 4.10).

CONCLUSIONS

Despite a model adequately powered to identify 10-20 statistically significant predictors, none were found. Given the high prevalence of OSA in severely obese patients undergoing bariatric care, the lack of identifiable clinical predictors mandates that polysomnography be performed in all such patients clinically suspected to have OSA.

Supervisor: Dr. Raj Padwal

Table 1. Predictors of moderate-to-severe sleep apnea¹

Variable	β -Coefficients	Odds ratio	95 % Confidence Interval
Age	-0.12	0.99	0.95 - 1.02
Sex	-0.39	0.68	0.25 - 1.83
BMI	0.21	1.02	0.98 - 1.06
Neck Circumference	0.79	1.08	0.99 - 1.18
Hypertension	0.67	1.95	0.92 - 4.10
ESS	-0.02	0.99	0.93 - 1.05
Diabetes	-0.47	0.62	0.28 - 1.37
Rhinosinusitis	-0.66	0.52	0.14 - 1.87
Depression	0.37	1.45	0.67 - 3.14
Smoking	0.73	2.07	0.40 - 10.80

¹Model c-statistic = 0.66

The SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure) Pilot Results

Eloisa Colin-Ramirez (BSc, PhD)¹, Finlay McAlister (MD, MSc)², Yinggan Zheng (MA, MEd)³, Sangita Sharma (PhD)³, Paul Armstrong (MD)², Justin A Ezekowitz (MBBCh, MSc)¹

Supervisor: Dr. Justin Adrian Ezekowitz

INTRODUCTION

Guideline recommended level of dietary sodium intake for heart failure (HF) patients is variable reflecting limited randomized controlled trial (RCT) evidence. The objective of this pilot study was to determine the feasibility of conducting a RCT comparing a low-sodium to a moderate-sodium diet in HF patients.

METHODS

Methods: HF patients (NYHA 2-3, any ejection fraction) recruited from the Heart Function Clinic at the Mazankowski Alberta Heart Institute were randomized to low (1500 mg/day) or moderate-sodium (2300 mg/day) diet. Patients received structured dietary counselling and menu plans; dietary intake was evaluated using 3-day food records. The endpoints were quality of life (KCCQ scores) and B-type natriuretic peptide (BNP) from baseline to 6 months of follow-up.

RESULTS

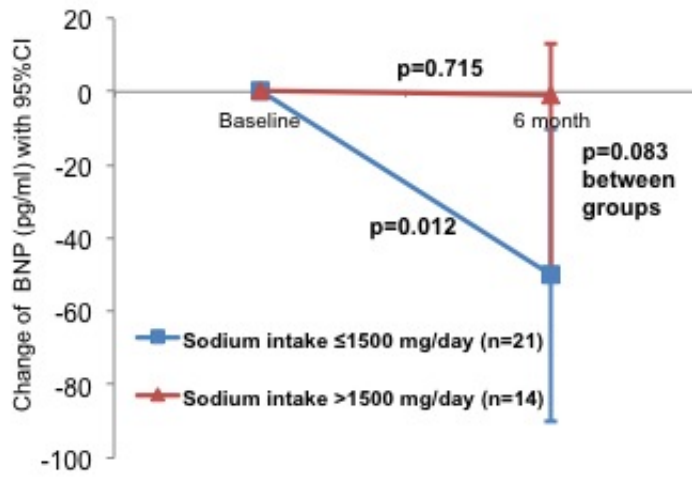
38 patients were enrolled (19/group). After 6 months, median sodium intake dropped from 2137 to 1398 mg/day in the low-sodium and 2678 to 1461 mg/day in the moderate-sodium diet group. Median BNP levels changed over 6 mo in the low-sodium diet group (216 to 71 pg/ml, Δ 51 pg/ml [-2,331], $p=0.006$) and in the moderate-sodium diet group (171 to 188 pg/ml, Δ 36 pg/ml [-51,62], $p=0.7$; $p=0.17$ between groups). Over 6m, median KCCQ scores increased in low-sodium diet group (63 to 75, Δ 9 [2,15], $p=0.006$), and trended to increase in the moderate-sodium group (66 to 73, Δ 6 [-1,15], $p=0.07$); $p=0.4$ between groups. At 6m, a post hoc analysis based on the dietary sodium intake achieved ($>$ or \leq 1500 mg/day) showed an association between achieved dietary sodium and improvement in BNP levels and KCCQ scores (Figure a and b, respectively).

CONCLUSIONS

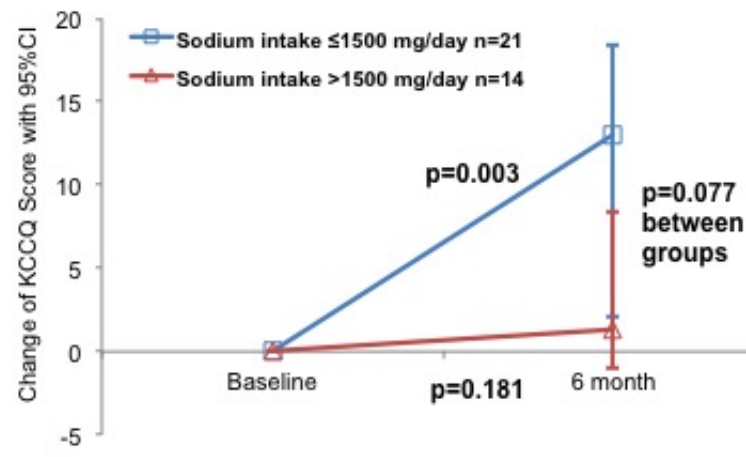
The dietary intervention was feasible and effective in reducing sodium intake in HF patients. A dietary sodium intake \leq 1500 mg/day was associated with lower BNP levels and improved quality of life in HF patients and informs the design of an adequately-powered, clinical event driven RCT.

Supervisor: Dr. Justin Adrian Ezekowitz

(a) BNP



(b) KCCQ



Update on Community-driven Research on H. pylori infection in the Canadian Arctic.

Sanjay Beesoon, Emily V Hastings, SJO Veldhuyzen van Zanten, Karen J Goodman,
CANHelp Working Group
Supervisor: Dr Karen Goodman

INTRODUCTION

Introduction. Estimates suggest that half of the world population is infected with *Helicobacter pylori*, associated with increased risk of peptic ulcers and gastric cancer, which have important societal and economic costs. Since 2007, the Canadian North *Helicobacter pylori* (CANHelp) Working Group has linked Arctic Aboriginal communities with health officials and University of Alberta investigators to address community concerns regarding this infection.

METHODS

On behalf of community leaders who advocated for research aimed at reducing the occurrence of *H.pylori* infection, Northwest Territories (NWT) health officials asked University of Alberta health scientists to help them characterize the disease burden and develop strategies to better manage this infection. With community engagement in research planning, the CANHelp Working Group initiated a project in Akalvik, NWT, with *H.pylori* screening, collection of risk factor data, histopathology of gastric biopsies, and an antibiotic treatment trial; similar projects followed in Tuktoyaktuk NWT, Fort McPherson NWT and Old Crow, Yukon Territory. We report here key results to date.

RESULTS

The prevalence of *H.pylori* infection ranged from 56-68% across the four communities, higher than the 20-30% observed in southern Canadian populations. Among *H.pylori*-positive participants, the prevalence range across communities was 38-65% for severe gastritis and 21-74% for gastric atrophy, in contrast to 5% with severe gastritis and 2% with atrophy among *H.pylori*-positive residents of Alberta who had biopsies examined at the University of Alberta Hospital pathology laboratory.

CONCLUSIONS

This community-driven research shows high prevalence of *H.pylori* infection, severe chronic gastritis, and gastric atrophy. Given that chronic inflammation and atrophy are believed to increase the risk of gastric carcinoma, concern in the participating communities about health risks from *H.pylori* infection appear warranted. Ongoing research will continue to generate information sought by participating communities and by the decision makers who provide their health care.

Supervisor: Dr Karen Goodman

Hematoma contraction in acute intracerebral hemorrhage is associated with poor prognosis.

Mahesh P Kate, Matthew Boyko, Laura Gioia, Bronwen Gould, Rebecca McCourt, Micheal Hill, Negar Asdaghi, Dariush Dowlatahahi, Shelagh Coutts, Andrew Demchuk, Brian Buck, Ashfaq Shuaib, Kenneth Butcher
Supervisor: Kenneth Butcher

INTRODUCTION

Dynamic changes occur in the intracerebral hemorrhage(ICH) in first 72 hours. Variably 13-27% of patients have hematoma expansion in first 24 hours depending on the definition. Hematoma contraction has been described in 24-72 hours period after symptom onset but not in the first 24 hours. We hypothesize that hematoma contraction rarely occurs in the first 24 hours.

METHODS

In the ICH Acutely Decreasing Arterial Pressure Trial (ICH ADAPT), patients with ICH <24 hours duration were randomized to two systolic BP(SBP) target groups (<150 mmHg vs. <180 mmHg). Computed tomography(CT) perfusion imaging was performed 2 h post-randomization. Two blinded assessors, planimetrically measured hematoma volumes and perihematoma edema at baseline, 2 and 24 hours after randomization(Inter-class coefficient=0.92). Intraparenchymal(IPH), intraventricular (IVH) and total hematoma volumes were assessed at all the three time points. Stable hematoma(SH), Hematoma expansion(HE) and hematoma contraction(HC) cut-off was pre-defined as no change, ≥ 3 ml increase or decrease respectively from the baseline total hematoma volume to 24 hours CT scan.

RESULTS

Seventy patients were included for the analyses with mean (SD) age of 69.74(11.92) years and median(IQR) ICH volume of 16.71(22.61) ml. HE and HC occurred in 27.1 % (19/70) and 5.7%(4/70) respectively. The baseline median ICH volumes in SH, HE and HC were 10.56(14.43), 27.97(47.46) ml and 37.22(56.21)ml($p < 0.0001$) respectively. The median difference in the ICH volume for the SH, HE and HC between baseline and 24 h were 0.32(1.31) ml, 12.56(23.21) ml and 5.67(11.22)ml($p < 0.0001$). There is no difference in baseline systolic BP, 2h systolic BP, perihematoma relative cerebral blood flow and relative cerebral blood volume among groups. The Barthel index at 90 days in SH, HE and HC were median of 95(41), 0(26) and 50(100)($p = 0.001$).

CONCLUSIONS

Hematoma contraction occurs in a small proportion of patients in ICH. Patients with HC have higher baseline ICH volume and poor prognosis thereof.

Supervisor: Dr. Kenneth Butcher

A potential right ventricle-specific mechanism for heart failure: the miR-208/Mef2c axis.

Roxane Paulin, Gopinath Sutendra, Vikram Gurtu, Peter Dromparis, Adam Kinnaird and Evangelos D. Michelakis
Supervisor: Dr Evangelos D. Michelakis

INTRODUCTION

Right Ventricular Failure (RVF) is a major cause of morbidity and mortality in pulmonary hypertension (PHT), but its mechanism remains unknown. Myocyte enhancer factor 2 (Mef2) has been implicated in RV development, regulating metabolic, contractile and angiogenic genes. Moreover, Mef2 regulates microRNAs (miRNAs) that have emerged as important determinants of cardiac development and disease, but for which the role in RV is still unclear. We hypothesized a critical role of a Mef2-miRNA axis in RVF.

METHODS

We used an in vivo rat PHT model (monocrotaline), in which we studied RV free-wall tissues from rats with normal (nRV), compensated (cRVH) and de-compensated (dRVH) RV hypertrophy, carefully defined based on clinically-relevant parameters, including: RV systolic and end-diastolic pressures, cardiac output, RV size and survival. We also performed mechanistic in vitro experiments using isolated adult rat cRVH cardiomyocytes. Standard cellular and molecular techniques like Western Blotting, immunostaining and qRT-PCR were used.

RESULTS

Mef2c expression was sharply increased in cRVH tissues, but was lost in dRVH, a phenomenon likely responsible for dRVH. An unbiased screening of miRNAs identified a short miRNA signature of dRVF. Included was the myocardium-specific miR-208, progressively downregulated as RVF progresses, in contrast to what is described in left ventricular failure. A target of miR-208, MED13, is a subunit of the complex mediator of transcription, and associates with the repressor NCoR1, known to decrease Mef2c transcriptional activity. Their expressions were increased in dRVH. In vitro, miR-208 inhibition (using an adenovirus expressing an anti-miR-208) activated the MED13/NCoR1 axis, promoting in turn Mef2 inhibition, closing a self-limiting feedback loop and driving the transition from cRVH toward dRVH. In our model, serum miR-208 levels were decreased, mirroring the levels measured in RV myocardium tissues.

CONCLUSIONS

We describe a novel RV-specific mechanism for RVF, which could potentially lead to new biomarkers and therapeutic targets.

Supervisor: Dr Evangelos D. Michelakis

Cardiac Risk Evaluation in Moderate to Severe Inflammatory Arthritis Patients

Zainab Alabdurubalnabi
Supervisor: Dr. Stephanie Keeling

INTRODUCTION

Increased cardiovascular (CV) risk is well-recognized in rheumatoid (RA) and psoriatic arthritis (PSA) patients and is felt to be secondary to inflammation and traditional CV risk factors. This study evaluates self-reported traditional CV risk factors in a population of moderate to severe inflammatory arthritis (IA) patients on biologic therapies.

METHODS

A questionnaire evaluating features of IA disease, treatments and self-reported traditional CV risk factors was mailed to patients who had consented to be part of the RAPPORT database (Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics). Patients were asked complete fasting labs and were invited to participate in the Cardiovascular Risk Reduction Clinic for Inflammatory Rheumatic Diseases (CRRC - IRD). Questionnaire results were entered into a Microsoft excel database with descriptive statistics.

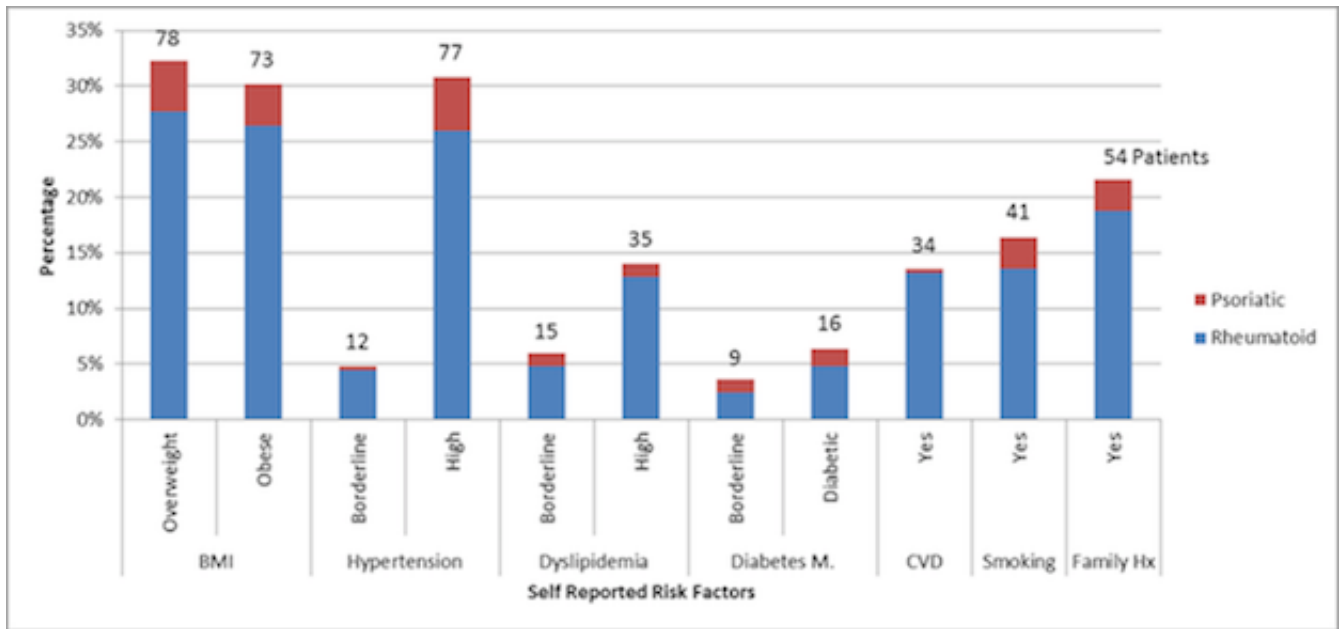
RESULTS

Two-hundred and fifty (250) questionnaires (M:F 76:174) were returned, mean age 60 (SD 12), with 224 rheumatoid arthritis (RA) and 26 psoriatic arthritis (PsA) patients. Mean disease duration was 17.5 years (SD 13.5). Any life-time exposure (past/current) to IA-related medications included: prednisone 139(55%); non-steroidal anti-inflammatories (NSAIDs) 166(66%); TNF inhibitors 244(96%); rituximab 22(9%); abatacept 25(10%); and tocilizumab 11(4%). The mean number of traditional CV risk factors (age, gender, hypertension, diabetes, dyslipidemia, smoking, personal history of CV disease, family history of early CV disease and obesity) per patient was 2.53(SD 1.51). The burden of traditional CV risk factors is described in Figure 1. Four patients who had not reported diabetes had HBA1c in the diabetic range. History of cardiac disease was reported by 34(14%) of patients. Fasting cholesterol profile (mmol/L) [mean (SD)] included: total cholesterol 4.5 (1), LDL 2.9 (0.8), HDL 1.5 (0.4), total cholesterol/HDL 3.5 (0.9).

CONCLUSIONS

Moderate to severe IA patients have a large burden of CV disease. CV risk reduction and aggressive IA management strategies should be emphasized. Untreated comorbidities remain an important problem that should not be overlooked.

Supervisor: Dr. Stephanie Keeling



Safety and Effectiveness of Mycophenolate in the Treatment of Systemic Sclerosis: A Systemic Review

Abdulaziz Alahmadi , Mohammed A. Omair and Sindhu R. Johnson
Supervisor: Sindhu R. Johnson

INTRODUCTION

Background:

There has been an increased interest in the use of mycophenolate mofetil (MMF) and mycophenolate sulphate (MS) in the treatment of patients with systemic sclerosis (SSc) with concerns about safety.

Objective:

To systematically evaluate the safety and effectiveness of MMF or MS in the treatment patients with SSc.

METHODS

A literature search of the published literature was conducted through the following databases: Medline, EMBASE, Cochrane library and CINAHL. Any peer reviewed article reporting the safety and/or effectiveness of MMF or MS in patients with SSc was included. Two investigators independently evaluated the abstracts.

RESULTS

A total of 616 citations were identified. Twenty articles fulfilled the inclusion and exclusion criteria and were included in the analysis. MMF was used in 19 studies and MS in 1 study. Mycophenolate compounds were used as induction in 14 studies, as maintenance in 17 studies and as induction and maintenance in 15 studies. A total of 477 patients have been reported to be exposed to either MMF or MS. Overall 89 (18.7) AE's of those 43(9%) patients developed GI AE's. The reported percentage of AE's occurring in SSc patients ranged from 0-21.4%. Forty six (9%) non-GI AE's occurred. Eight studies evaluated MMF/MS in treating skin disease, 5 of them reported a significant improvement in the MRSS, while 12 studies evaluated their effect on lung function all studies reported a stabilization but only on study reported a significant improvement in the FVC and another on the DLCO.

CONCLUSIONS

MMF and MS are effective in treating skin disease in patients with SSc. In patients with lung involvement pulmonary function test stabilized or improved but not reaching statistical significance. The safety profile of these medications is comparable with what has been reported in the transplant and lupus literature.

Supervisor: Dr. Sindhu R. Johnson

Do Outcomes for Patients With Heart Failure Vary by Emergency Department Volume?

Sandeep Brar MD; Finlay A. McAlister MD, MSc; Erik Youngson MMath; Brian H. Rowe MD, MSc
Supervisor: Dr. Finlay A. McAlister

INTRODUCTION

Heart failure is a common Emergency Department (ED) presentation but whether ED volume influences patient outcomes is unknown.

METHODS

Retrospective cohort of all adults presenting to 93 EDs between 1999 and 2009 with a most responsible diagnosis of heart failure (n=44 925 ED visits; mean age, 76.4 years).

RESULTS

Cases seen in low-volume EDs had less comorbidities and were less likely to be hospitalized (54.5%) than those seen in medium (61.8%; adjusted odds ratio [aOR] 1.16, [95% confidence interval {CI} 1.10–1.23]) or high-volume EDs (73.6%; aOR, 1.95 [95% CI, 1.83–2.07]). Of patients treated and released, low-volume ED cases exhibited higher risk of death/hospitalization/ED visit in the subsequent 7 (22.0%) and 30 days (44.9%) than medium (16.3%; aOR, 0.81 [95% CI, 0.73–0.90], and 35.3%; aOR, 0.79 [95% CI, 0.73–0.86]) or high-volume ED cases (13.0%; aOR, 0.69 [95% CI, 0.61–0.78], and 30.2%; aOR, 0.67 [95% CI, 0.61–0.74]). Of patients hospitalized at the time of their index ED visit, low-volume ED cases exhibited a higher risk of 30-day death/all-cause readmission (24.3%) than those seen in medium (21.9%; aOR, 0.83 [95% CI, 0.76–0.91]) or high-volume EDs (18.1%; aOR, 0.77 [95% CI, 0.70–0.85]).

CONCLUSIONS

Low-volume EDs were more likely to discharge patients with heart failure home, but low-volume ED cases exhibited worse outcomes (driven largely by readmissions or repeat ED visits). Interventions to improve management of acute heart failure are required at low-volume sites.

Supervisor: Dr. Finlay A. McAlister

Prosthetic joint infection rates and risk factors following shoulder arthroplasty: a retrospective review

Justin Chen, Martin Bouliane, Joseph Bergman, Stephanie Smith
Supervisor: Dr. Stephanie Smith

INTRODUCTION

There is emerging data to suggest *Propionibacterium acnes* may be involved in shoulder infections more commonly than *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp (CNS). If the majority of prosthetic shoulder infections are caused by *P. acnes* and CNS, an alternative antibiotic for perioperative prophylaxis may need to be considered as standard cefazolin may not have reliable activity against these pathogens. The objectives of this study were to examine the infection rates and microbiology of prosthetic shoulder joint infections at two large tertiary care centres from 2001 to 2011 in order to determine the most appropriate perioperative antimicrobial prophylaxis for this type of surgery.

METHODS

This was a retrospective chart review examining all patients age 18 years and older who have had total or hemi shoulder arthroplasty at two high volume centres in Edmonton, Alberta, Canada from January 1, 2001 to December 31, 2011. Patient charts were reviewed for three years from the time of initial surgery to look for evidence of shoulder infection. Pertinent data was collected for all infected cases which included demographics, comorbidities, perioperative antibiotic administration, duration of procedure, and non-infectious complications that occurred while in hospital. Descriptive data such as implicated pathogen, management, and outcomes was also recorded.

RESULTS

There were 10 cases that met criteria as prosthetic joint infections post-shoulder surgery out of total 555 primary shoulder arthroplasties resulting in an overall infection rate of 1.8 per 100 surgeries. The most common organisms isolated were *P. acnes* (3) and CNS (3).

CONCLUSIONS

The infection rate for total and hemi arthroplasty surgeries over the ten year period was found to be 1.8 per 100 surgeries. The most common organisms isolated were *P. acnes* and CNS. Combination clindamycin and vancomycin may be a more appropriate choice for surgical prophylaxis in patients who are at higher risk for infection.

Supervisor: Dr. Stephanie Smith

Health Care Costs Associated With Acute Kidney Injury

David Collister, MD¹, Neesh Pannu, MD, SM¹, Feng Ye, Msc¹, Matthew James, MD, PhD², Brenda Hemmelgarn, MD, PhD², Betty Chui, MD, MSc³, Scott Klarenbach, MD, Msc^{1,4}

Supervisor: Dr. Scott Klarenbach

INTRODUCTION

The association of AKI with health care costs is unclear. The objective of this study was to quantify health care costs of AKI by severity and renal recovery.

METHODS

We identified a cohort of adults hospitalized in Alberta for <60 days between November 2002 and December 2008, and used serum creatinine to define AKI. Patients with ESRD or eGFR <15ml/minute/1.73m² were excluded. Costs were determined from inpatient, outpatient, and physician claims data over index hospitalization, renal recovery period (1-90 days) and 3-12 months post admission. A fully adjusted GLM regression model with bootstrapping was used, and sensitivity analysis was performed.

RESULTS

Of 229869 subjects (mean age 62.8 years, 47% male), 24494 (10.7%), 4401 (1.9%), 2390 (1.0%) and 847 (0.4%) had AKIN stages 1, 2, 3 without dialysis, and 3 with dialysis, respectively. Increasing severity of AKI was independently associated with length of stay and costs (Table 1). Over 3-12 months, AKIN 3 requiring dialysis that either recovered, or did not recover was associated with the greatest costs (\$18096 and \$30166 respectively), with dialysis specific costs accounting for 43.1% of costs for those that did not recover at 90 days.

CONCLUSIONS

Graded increases in costs are observed with increasing severity of AKI, greatest with AKI requiring dialysis. AKI is associated with increased cost over 3-12 months, most pronounced for AKIN 3 requiring dialysis with non-recovery. The costs associated with AKI warrant evaluation of potential strategies to prevent and attenuate AKI or promote renal recovery.

Supervisor: Dr. Scott Klarenbach

Table 1: Length of Stay, Mean and Incremental Costs by AKI Status (fully adjusted)

AKI = acute kidney injury, AKIN = Acute Kidney Injury Network, LOS = length of stay, CI = confidence interval

	No AKI (86.0%)	AKIN 1 (10.7%)	AKIN 2 (1.9%)
Hospitalization LOS (days)			
Mean (95% CI)	8.9 (8.9, 9.0)	11.4 (11.3, 11.6)	12.7 (12.4, 13.1)
Incremental (95% CI)	Reference	+2.5 (1.0, 4.0)	+3.8 (2.8, 4.8)
Hospitalization (\$)			
Mean (95% CI)	9433 (9389, 9477)	12291 (12113, 12470)	14310 (13884, 14736)
Incremental (95% CI)	Reference	+2858 (2674, 3042)	+4877 (4449, 5305)
Admission to 90 days (\$)			
Mean (95% CI)	15409 (15344, 15474)	19183 (18957, 19409)	21158 (20518, 21797)
Incremental (95% CI)	Reference	+3774 (3539, 4009)	+5748 (5106, 6391)
	No AKI (88.1%)	AKIN 1-3 no dialysis Recovered (7.3%)	AKIN 1-3 no dialysis No Recovery (3.8%)
3-12 months (\$)			
Mean (95% CI)	9163 (9061, 9264)	11062 (10613, 11511)	11514 (10944, 12084)
Incremental (95% CI)	No reference	+1900 (1439, 2360)	+2352 (1772, 2931)

Serum drug levels of isoniazid and rifampin as a predictor of 2 month sputum culture results in patients with M. tuberculosis infection

Mah A., Kharrat H., Ahmed R., Gao Z., Der E., Hansen E., Long R., Kunimoto D., Cooper R.

Supervisor: Dr. Ryan Cooper

INTRODUCTION

Therapeutic drug monitoring is often utilized to assess treatment adequacy and guide management decisions. Serum drug levels (SDL) for anti-mycobacterial medications have been measured in Northern Alberta for over a decade. We undertook a review of tuberculosis cases with available SDL for isoniazid (INH) and/or rifampin (RIF) to assess the relationship between adequacy of SDL and 2 month culture results and to determine any variables associated with low SDL in our population.

METHODS

A retrospective review was performed of cases of tuberculosis in Northern Alberta with available SDL's. Data collected included sex, country of origin, smear positivity, cavitation, weight, BMI, comorbidities, 2-month sputum culture results and treatment outcome in addition to SDL's. Cases were deemed to have adequate or inadequate SDL based on the maximum concentration (C_{max}) of drug achieved in the serum and variables were then compared between groups.

RESULTS

We found a statistically significant increase in 2 month sputum culture positivity ($p=0.0084$) in the cohort with inadequate levels of INH and a similar trend in the cohort with inadequate levels of RIF ($p=0.0725$). As well, insulin dependent diabetes was associated with low concentrations of INH (0.048), and increased weight was associated with low concentrations of RIF ($p=0.02$).

CONCLUSIONS

Low serum drug concentrations of INH and to a lesser extent RIF appear to be associated with increased sputum positivity at 2 months. Further prospective studies are required to confirm this association.

Supervisor: Dr. Ryan Cooper

CARDIOVASCULAR OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS, PSORIASIS AND PSORIATIC ARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSES

Alexandra McFarlane, Stephanie Keeling, Ben Vandermeer, Canadian Dermatology Rheumatology Co-morbidity Initiative members
Supervisor: Stephanie Keeling

INTRODUCTION

Rheumatoid arthritis (RA), psoriasis (PsO) and psoriatic arthritis (PsA) are associated with increased risk of CV-mortality but less clearly related to specific cardiovascular outcomes (CVO). The purpose of the study was to evaluate important CVO in RA, PsO and PsA patients.

METHODS

Medline, Embase, Cochrane and abstracts from ACR/EULAR/AAD/EADV were searched for in English language full-length articles and abstracts published from 1960 up to January 15, 2013 describing CVO in observational studies in RA, PsO and PsA patients, compared to a control group. Outcomes included all-cause and CV-mortality, and specific CVO including myocardial infarction (MI)/acute coronary syndrome (ACS), cerebrovascular accident (CVA - including stroke or transient ischemic attack), heart failure (HF) and peripheral artery disease (PAD). Random effects meta-analyses were performed.

RESULTS

Out of 3457 references identified, 127 observational studies (RA=89; PsO=27;PsA=11) met our inclusion criteria. Important effect size estimates represented as standardized mortality (SMR) and morbidity (SMoR) ratios are listed in Table 1. Some papers were eliminated from statistical analysis on the basis of inadequate data provided.

CONCLUSIONS

RA, PsO and PsA are associated with several important CVO's including less reported outcomes such as PAD, CVA and HF. These complications may be less recognized by physicians. Fewer studies exist for PsA but CVO's appear increased overall. Risk reduction strategies should be considered.

Supervisor: Dr. Stephanie Keeling

Table 1
Effect Size Estimates for Important Cardiovascular Outcomes

CVO	RA	PsO	PsA
Fatal CVO	SMR	SMR	SMR
All-cause mortality	1.59 (1.47-1.71)	1.43 (1.14-1.81)	1.46 (1.03-2.07)
CV-mortality	1.58 (1.47-1.70)	1.32 (1.12-1.57)	1.61 (1.09-2.38)
Specific CVO	SMoR	SMoR	SMoR
MI/ACS	1.85 (1.55-2.22)	1.23 (1.07-1.42)	1.55 (0.57-4.21)
CVA	1.56 (1.26-1.94)	1.18 (1.06-1.32)	0.91 (0.34-2.43)
PAD	1.95 (1.05-3.63)	1.31 (1.17-1.45)	1.53 (1.20-1.94)
HF	1.54 (1.29-1.83)	1.35 (1.13-1.63)	1.43 (1.08-1.90)

Gastroesophageal reflux, esophageal motility and lung function in patients with idiopathic pulmonary fibrosis

Cheryl Laratta (1), Ali Kapasi (2), Adriana Lazarescu (3), Meena Kalluri (2)
Supervisor: Dr. Meena Kalluri

INTRODUCTION

Esophageal motility disorders and gastroesophageal reflux (GER) are common in patients with end-stage lung disease including IPF. GER-induced aspiration has been proposed as a risk factor for development of IPF and may contribute to further lung injury. Recognition of subtle manifestations of GER in this population is therefore imperative.

METHODS

We performed a retrospective data review of patients with idiopathic pulmonary fibrosis (IPF) referred for combined 24-hour pH-impedance and high resolution esophageal manometry studies between 2009 and 2013 from an IPF clinic and a pre-lung transplant clinic.

RESULTS

Twenty-five patients were included, 68% male, age 64 ± 1.4 years, with a mean total lung capacity (TLC) of $61.1 \pm 2.5\%$ predicted. Fifty-six percent of patients had abnormal high resolution manometry: 36% of all patients had ineffective esophageal motility (IEM), 20% had weak upper esophageal sphincters, 12% had weak lower esophageal sphincters (LES), 12% had elevated LES resting pressures, and 28% had a hiatus hernia. Four of the 25 patients (20%) reported dysphagia or regurgitation (sensitivity 27%, specificity 100%). Fourteen patients had symptoms of reflux, of whom three had a Demeester score >14.7 . Symptomatic GER was not associated with manometric abnormalities. Patients with esophageal symptoms had a trend towards association with presence of IEM ($p=0.081$) when compared to those without esophageal symptoms. Patients with IEM had a trend towards increased TLC as compared to those without ($66.4 \pm 3.0\%$ predicted vs $58.1 \pm 3.3\%$ predicted, $p=0.11$), although there was no difference in diffusion capacity of carbon monoxide adjusted for alveolar volume (50.4 ± 4.50 mL/min/mmHg/L vs 56.5 ± 4.0 mL/min/mmHg/L, $p=NS$).

CONCLUSIONS

Esophageal motility is frequently abnormal in patients with IPF. Esophageal symptoms were insensitive but specific for abnormalities on esophageal manometry, and may be associated with IEM. These findings need to be confirmed with a larger study cohort.

Supervisor: Dr. Meena Kalluri

Crohn's disease outpatients treated with adalimumab have an earlier loss of response and requirement for dose intensification compared to infliximab

Christopher Ma, Vivian Huang, Darryl K. Fedorak, Karen I. Kroeker, Levinus A. Dieleman, Brendan P. Halloran, and Richard N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Efficacy of biologic agents targeting tumour necrosis factor alpha in maintaining remission in Crohn's disease (CD) patients may wane with time, leading to secondary loss of response that can often be overcome with dose escalation. Direct comparison of secondary loss of response of adalimumab and infliximab during long-term treatment of CD in a real-life IBD clinic has not been previously evaluated.

METHODS

A retrospective cohort study evaluating outpatients with CD on a maintenance regimen with adalimumab or infliximab from 2004-2013 and experiencing a secondary loss of response was conducted. All infliximab-treated patients were anti-TNF naïve. Adalimumab-treated patients were stratified by prior anti-TNF exposure. Kaplan-Meier analysis determined time to loss of response and multivariate regression identified risk factors for loss of response.

RESULTS

218 CD patients met inclusion criteria (117 infliximab, 101 adalimumab). Mean follow-up duration was 179.5 weeks for infliximab and 152.8 weeks for adalimumab.

51.3% (60/117) of infliximab patients, 60.5% (23/38) of adalimumab patients naïve to anti-TNF therapy, and 65.1% (41/63) of adalimumab patients with prior anti-TNF exposure developed secondary loss of response. Median time to secondary loss of response was longer for infliximab patients (99.3 weeks, IQR 55.7-168.5 weeks) compared to both adalimumab patients naïve to anti-TNF therapy and adalimumab patients with prior anti-TNF exposure (58.9 and 52.7 weeks, respectively).

In multivariate regression, concurrent azathioprine or methotrexate was associated with lower risk of loss of response (aOR 0.32, 95%CI: 0.11-0.91) while moderate/severe disease activity (Harvey Bradshaw index ≥ 7) at induction was associated with higher risk of loss of response (aOR 3.15, 95%CI: 1.17-8.49).

CONCLUSIONS

Over 50% of CD patients treated with infliximab and adalimumab developed secondary loss of response. Time to loss of response was significantly shorter in patients treated with adalimumab compared to infliximab and prior anti-TNF exposure further accelerated time to loss of response.

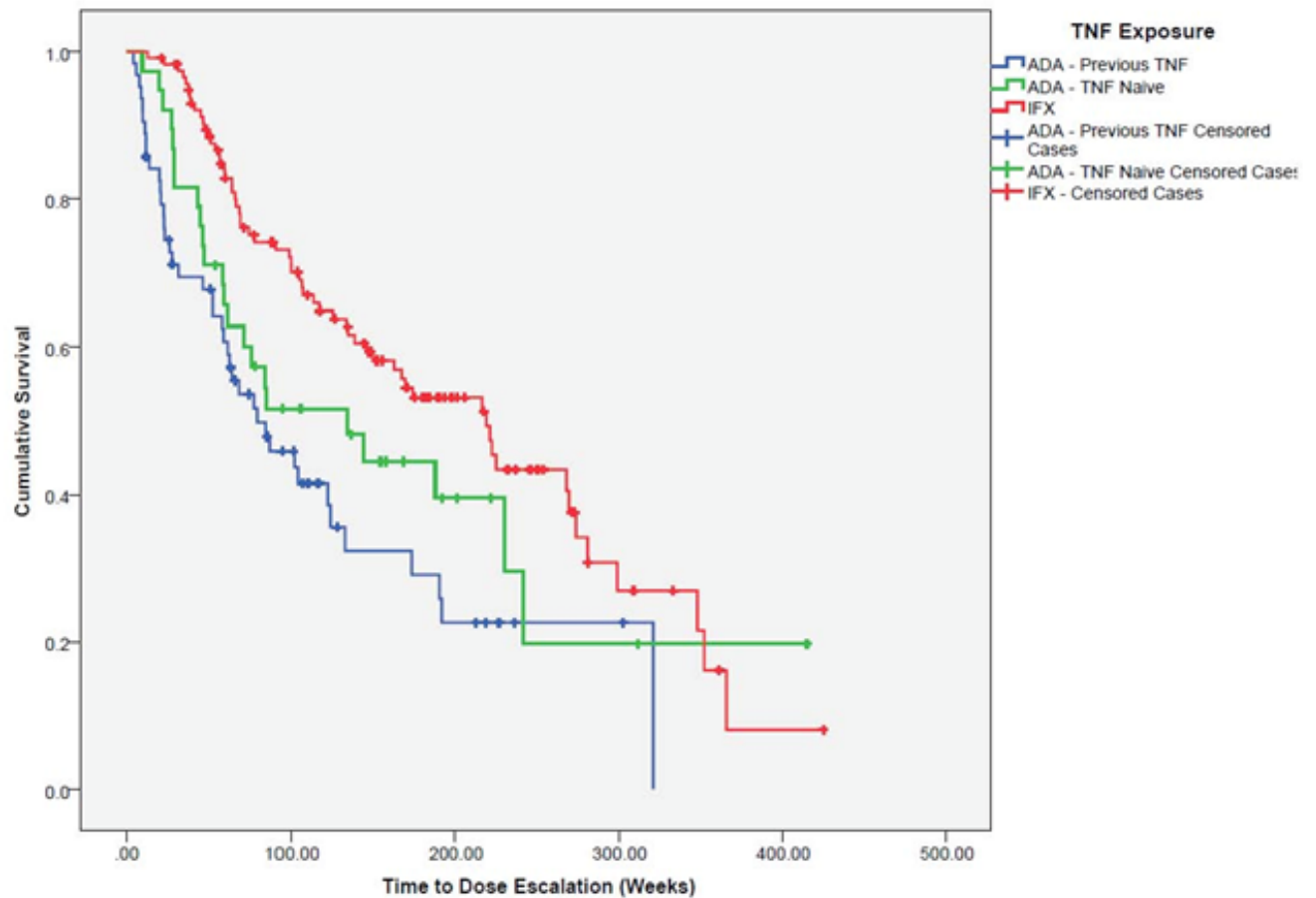


Figure 1 – Kaplan-Meier survival curves of secondary loss of response during maintenance therapy requiring dose escalation for infliximab (red) versus TNF naïve adalimumab (green) and adalimumab with prior anti-TNF exposure (blue). Hashed lines indicate censored cases (maintained response to last follow-up). $p < 0.01$ for infliximab compared to either adalimumab group. $p = 0.195$ for adalimumab with previous anti-TNF exposure compared to adalimumab naïve to anti-TNF therapy.

The Association Between Meteorological Events and Acute Heart Failure: New Insights from ASCEND-HF

Debraj Das, Jeffrey Bakal, Paul W. Armstrong, and Justin Ezekowitz
Supervisor: Dr. Justin Ezekowitz

INTRODUCTION

With the global prevalence of heart failure (HF) rising and the change in world climate the relationship of HF to climatic conditions is of increasing interest. Our objective was to examine the temporal relationship between meteorological conditions that may catalyze the presentation of a HF event.

METHODS

We used data from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, which involved 7141 patients at 398 sites in 30 countries. Each site was linked to a local weather station. Parameters including temperature and humidity were normalized by location for the 37 days prior to the enrolling HF event. Meteorological events were classified as a change in any parameter that occurred less than 10% of the time compared to the expected baseline. The seven days prior to the HF event were subdivided for analysis: T1 - the day of and -1 day; T2 - 2 and 3 days; T3 - 4 and 5 days; and T4 - 6 and 7 days (Figure). Results are reported as ratios of observed to expected weather events for each meteorological variable at the time of presentation.

RESULTS

Overall in T1 there were 10% fewer decreases in average [OR-0.91 95%CI (0.83-0.98)] and minimum [0.90(0.82-0.97)] temperature but excess decreases in relative humidity [1.13(1.02-1.23)]. In T2 an excess number of increases in maximum [1.18(1.06-1.30)] and average [1.21(1.10-1.32)] were noted. Finally in T4 there were fewer increases [0.84(0.74-0.95)] in average temperature compared to expected trends.

CONCLUSIONS

Climatic fluctuations were most relevant in the immediate 72 hours prior to the enrolling HF event. Continued exploration of biometeorological trends in HF patients should inform the need for vigilance of meteorological changes and acute HF thereby contributing to healthcare system planning globally.

Supervisor: Dr. Justin Ezekowitz

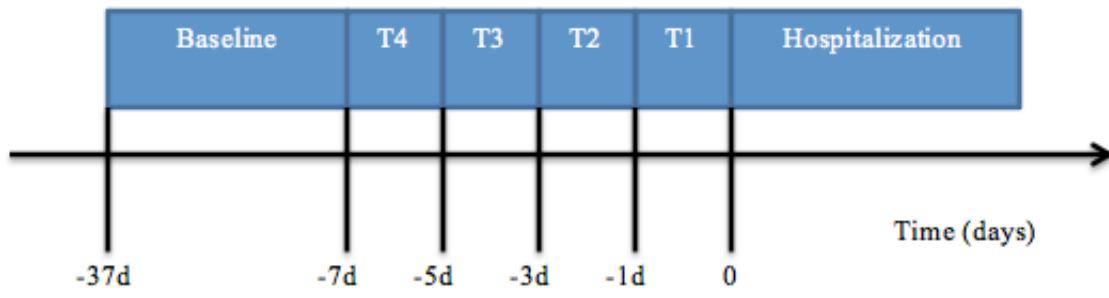


Figure: Time analysis subdivisions for the preceding 37 days prior to randomization

Assessing the validity of ICD-10 codes in the Emergency Department for Acute Heart Failure

Natalia Frolova, Jeff Bakal, Finlay McAlister, Brian Rowe, Justin Ezekowitz
Supervisor: Dr. Justin Ezekowitz

INTRODUCTION

Administrative database codes are used in population health research however the validity of the codes for acute heart failure (AHF) by International Classification of Disease-10 (ICD-10; AHF = I50.x) have not been adequately validated in the emergency department (ED).

METHODS

A cohort of 952 patients suspected of having AHF by ED physicians were prospectively recruited from 4 EDs in Edmonton, Canada from 2009-2012. Each patient had their diagnosis adjudicated using the Boston criteria and detailed chart review by expert physicians. ED and hospital admission ICD-10 codes were captured as the main diagnosis (MAIN) or in any diagnostic field (ANY). The predictive values, sensitivity, specificity and agreement were calculated with 95% confidence intervals.

RESULTS

849 patients were included in this analysis; median age was 77 years, 46% were female. The median BNP = 1017 pg/ml, median EF = 45%, median creatinine = 107 umol/L; 89% were admitted to hospital. Overall, 761 (89%) patients had AHF by Adjudicated Diagnosis. 73% (n=620) and 65% (n=583) had I50.x (MAIN) in the ED or at hospital discharge, respectively. Compared to Adjudicated Diagnosis, the positive and negative predictive value for I50.x as a MAIN diagnosis was 92.7% and 18.8%; sensitivity was 75.6% and specificity 48.9%. Compared to Adjudicated Diagnosis, the positive and negative predictive value for I50.x in ANY diagnosis was 91.4% and 22.2%; sensitivity was 89% and specificity 27.3%.

CONCLUSIONS

Receiving an ICD-10 I50.x diagnosis in the ED is highly predictive of AHF compared to expert reviewers. Reasons for misclassification need to be explored but are acceptable for use in outcomes research.

Supervisor: Dr. Justin Ezekowitz

Protein intake in cirrhotic patients on the liver transplant waiting list

Michael Ney, JG Abraldes, Mang Ma, Andrea Harvey, Puneeta Tandon
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Muscle mass depletion is associated with substantial morbidity and mortality in cirrhosis. Muscle loss is associated with several potentially modifiable factors, including insufficient dietary protein intake. Expert consensus suggests a protein intake of 1.2-1.5 g/kg/day. In a cohort of patients activated on the liver transplant waiting-list, it remains unclear a) what the baseline level of protein intake is and therefore how much room there is for modification, b) what predicts protein intake and c) whether low protein intake is a risk factor for mortality.

METHODS

Adults with cirrhosis who were evaluated for liver transplantation at a single tertiary care hospital between January 2000 and October 2009 were included. Estimated protein intake was derived from dietary records. Patients with insufficient protein intake data were excluded. Multivariate linear regression was employed to determine predictors of protein intake and mortality.

RESULTS

Of 742 potential patients, 112 were excluded due to insufficient information, leaving 630 patients for evaluation. Mean protein intake was 1.0 ± 0.36 g/kg/day and only 24% of patients met recommended intake guidelines. Multivariate analysis revealed two variables that were associated with lower protein intake - a higher Child-Pugh (CP) score and disease etiology. Twelve month mortality was 16% in patients consuming >0.8 g/kg/day and 28% in patients whose intake was <0.8 g/kg/day. Multivariate analysis revealed protein intake <0.8 g/kg/day, hyponatremia, elevated MELD and older age to be independent predictors of waiting-list mortality.

CONCLUSIONS

In a large cohort of cirrhotic patients awaiting liver transplantation, protein intake only met target in 24% of patients. Intake decreased with increasing CP class and in patients with Non-alcoholic fatty liver disease or Hepatitis C. Protein intake <0.8 g/kg/day, hyponatremia, high MELD and older age predicted mortality. Prospective intervention studies are required to determine whether protein supplementation has an impact on cirrhosis associated morbidity and mortality.

Supervisor: Dr. Puneeta Tandon

Acute coronary syndrome patients admitted to cardiology versus non-cardiology wards: Variations in treatment and outcome

Deirdre O'Neill MD, Danielle A. Southern MSc, Colleen M. Norris PhD, Blair J O'Neill MD, Michelle M Graham MD
Supervisor: Dr. Michelle Graham

INTRODUCTION

The development of Coronary Care Units (CCU) and treatment by cardiology services has previously been found to contribute to a reduction in mortality in acute coronary syndrome (ACS). We sought to evaluate investigation, therapy and outcomes of ACS patients admitted to non-cardiology wards in Southern Alberta.

METHODS

All patients with a positive troponin over a 2-year period in the Calgary Health Region were identified and subject to chart review to determine those with ACS diagnosis. Those admitted to non-cardiology wards were compared to ACS patients admitted to cardiology wards, using data from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database. Mortality up to 4-years was obtained through linkage to the Alberta Bureau of Vital Statistics.

RESULTS

From January 1, 2007 to December 31, 2008, 2105 troponin-positive ACS patients were identified, with 1636 (77.7%) admitted to cardiology and 469 (22.3%) to non-cardiology wards. Baseline characteristics are shown in table 1. Patients on non-cardiology wards rarely received a cardiology consult (5.1%) or transfer to cardiology (4.5%). Cardiac catheterization was underutilized (5.1% vs 86.4% of patients admitted to cardiology ($p < 0.0001$)). Significant differences existed in medications prescribed, with more patients on cardiology receiving evidence-based pharmacotherapy. Mortality for ACS patients admitted to non-cardiology wards was higher (in hospital 5.3% vs 1.6%, $P < 0.0001$), and longer term outcomes were worse at 30 days (OR 4.19 (95% CI 3.19, 5.49)), one year (OR 3.39 (95% CI 2.89, 3.99)) and 4 years (OR 2.80 (95% CI 2.48, 3.16)).

CONCLUSIONS

In a large, unselected ACS population in Southern Alberta, one quarter of patients are admitted to non-cardiology wards. These patients are older with more comorbidities, and rarely receive cardiology consultation or evidence-based pharmacotherapy. In addition, crude in-hospital and mortality up to 4-years is significantly higher than ACS patients admitted to a cardiology service.

Supervisor: Dr. Michelle Graham

Comorbidities	Cardiology Ward N=1,636	Non-Cardiology Ward N=469	P-value
Mean Age (Std. Dev.)	62.9 (13.4)	79.6 (11.9)	<0.0001
Male Sex	1,178 (72.0%)	240 (51.2%)	<0.0001
Cerebrovascular Disease	45 (2.75%)	93 (19.8%)	<0.0001
Diabetes	340 (20.8%)	151 (32.2%)	<0.0001
Hypertension	885 (54.1%)	218 (46.5%)	0.004
Dyslipidemia	317 (19.4%)	14 (3.0%)	<0.0001
Heart Failure	150 (9.2%)	176 (37.5%)	<0.0001
Renal Disease	85 (5.2%)	155 (33.0%)	<0.0001
Pulmonary Disease	67 (4.1%)	100 (21.3%)	<0.0001
Liver/GI Disease	13 (0.8%)	25 (5.3%)	<0.0001
Malignancy	26 (1.6%)	63 (13.4%)	<0.0001
Dementia	25 (1.5%)	66 (14.1%)	<0.0001
Sepsis/Shock	28 (1.7%)	18 (3.8%)	0.006
Bleed (GI, Intracranial, Urological, Pulmonary)	47 (2.9%)	56 (11.9%)	<0.0001
Pulmonary Embolism/DVT	9 (0.6%)	27 (1.6%)	<0.0001
Current Smoker	242 (14.8%)	22 (4.7%)	<0.0001
Prior MI	60 (3.7%)	23 (4.9%)	0.225

Physician Continuity Improves Outcomes for Heart Failure Patients Treated and Released From the Emergency Department

Robinder S. Sidhu, Erik Youngson, Finlay A. McAlister
Supervisor: Dr. Finlay McAlister

INTRODUCTION

Heart failure (HF) is a growing burden on the health care system responsible for over 1 million emergency department (ED) visits yearly in North America. Although most HF patients presenting to the ED are admitted to hospital, approximately 25-35% are discharged directly from the ED. Guidelines currently recommend early follow-up after hospital discharge, but it is unclear if early follow-up is beneficial in patients sent home from the ED and whether this follow-up should be with a familiar physician.

METHODS

Retrospective cohort study of all adults treated and released from 93 EDs in Alberta from 1999-2009 with a first time most responsible diagnosis of HF. Cox proportional hazards models with time varying covariates for post-ED outpatient visits were used.

RESULTS

In 12 285 patients (mean age 74.9 years), the rate of death or all-cause hospitalization at 6 months was lower in patients who saw a familiar physician (37.3%, aHR 0.89, 95%CI 0.83-0.96) in the first month versus those with no outpatient visits (58.1%) or visits only with unfamiliar physicians (40.2%). Taking into account all outpatient visits over each observation period and excluding those without follow-up, death or hospitalization was less common in those patients being followed by a familiar physician (aHR 0.79 [0.71-0.89] at 3 months, aHR 0.86 [0.77-0.95] at 6 months, and aHR 0.87 [0.80-0.96] at 12 months compared to unfamiliar physician follow-up). Any follow-up within 30 days of ED release was associated with a lower risk of repeat ED visit or death at 6 months (aHR 0.78 [0.73-0.82] for familiar physicians and 0.79 [0.72-0.86] for unfamiliar physicians).

CONCLUSIONS

Early follow-up after an ED visit for HF is associated with better outcomes, particularly with a familiar physician.

Supervisor: Dr. Finlay McAlister

Subfield-specific neuronal loss in hippocampal sclerosis: A systematic review and meta-analysis

Steve TA, Jirsch JD, Gross DW
Supervisor: Dr. Donald W Gross

INTRODUCTION

Hippocampal sclerosis (HS) is the most common pathological finding in medically refractory epilepsy. Classical HS is characterized qualitatively by severe neuronal loss in hippocampal subfield CA1, moderate involvement of CA3 and CA4, and sparing of CA2. However, the quantitative degree to which these subfields are involved in HS remains unclear. The present study, a systematic review and meta-analysis, was performed to quantify the magnitude, range, and variability of subfield-specific neuronal loss in HS.

METHODS

Studies were identified by searching the Medline and Embase databases using the search terms: cell count, hippocampus, and epilepsy. Of the 192 studies identified by the literature search, seven met all inclusion (both patients with HS and healthy controls studied, neuronal cells in CA1-4 identified, neuronal counts reported as mean and standard deviation) and exclusion criteria (sample size < 4 in either group, review articles, animal studies, previously reported data). Random effects meta-analyses were performed, comparing: i) neuronal densities in control (n=121) versus HS (n=371) groups for subfields CA1-4; and ii) amount of neuronal loss in HS between subfields CA1-4.

RESULTS

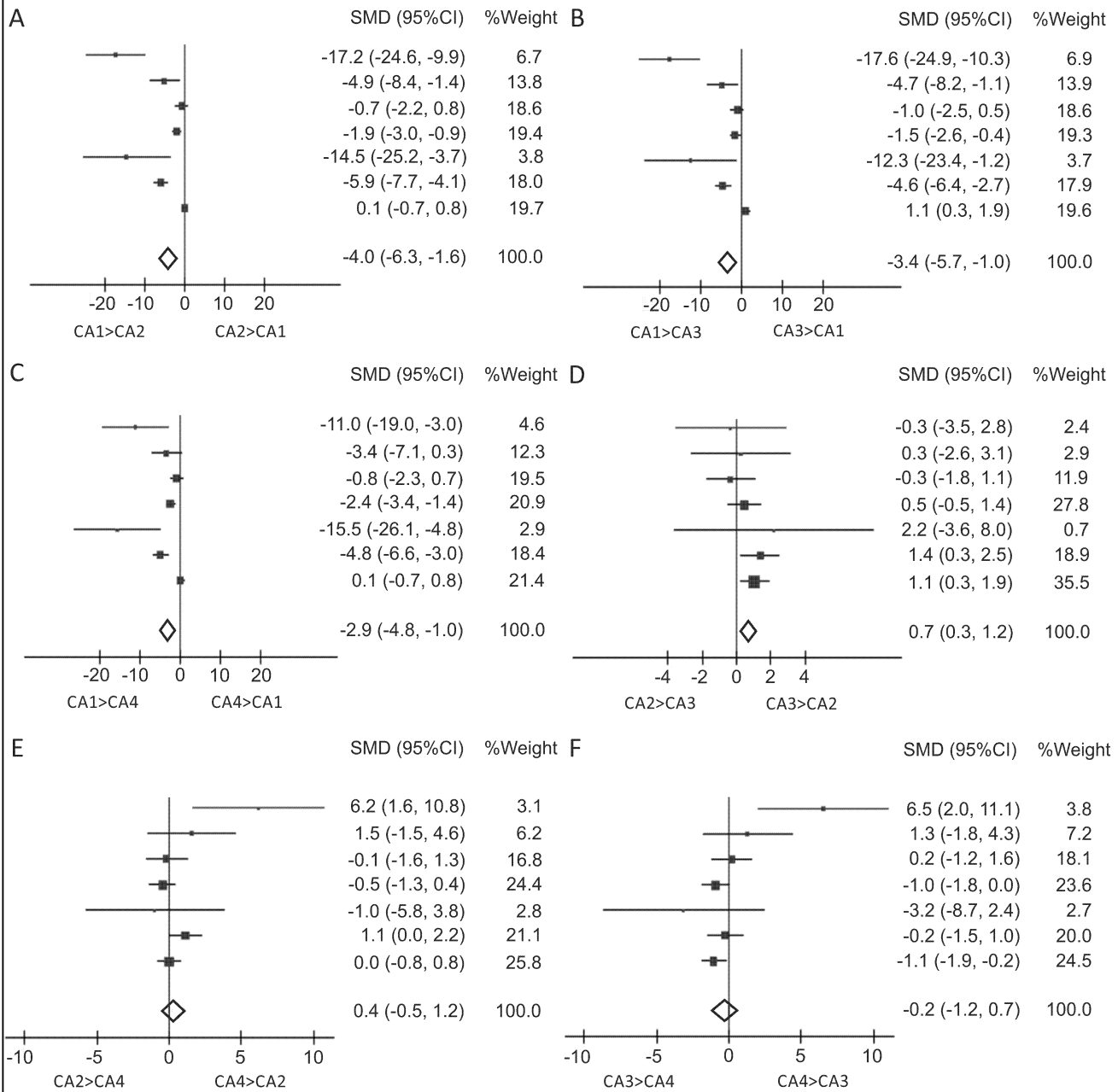
Statistically significant neuronal loss was observed comparing HS to control groups in all subfields ($p < 0.001$ for all comparisons). Significantly greater neuronal loss was demonstrated in HS comparing CA1 versus CA2 ($p < 0.001$), CA3 ($p = 0.005$), and CA4 ($p = 0.003$). Greater neuronal loss was also demonstrated in CA3 relative to the CA2 subfield ($p = 0.003$).

CONCLUSIONS

Our results show that HS is characterized by: i) neuronal loss in all hippocampal subfields (including CA2); and ii) greater pyramidal cell loss in CA1 than all other subfields (CA2-4).

Supervisor: Dr. Donald W Gross

Figure 3: Subfield-specific neuronal loss in hippocampal sclerosis



Standardized mean differences (SMD) and 95% confidence intervals (95% CI) are illustrated comparing magnitude of neuronal cell loss between subfields CA1-4 in hippocampal sclerosis. Significantly greater neuronal loss was demonstrated in CA1 versus CA2 (SMD -4.0; 95% CI -6.3, -1.6; $p < 0.001$), CA1 versus CA3 (SMD -3.4; 95% CI -5.7, -1.0; $p = 0.005$), CA1 versus CA4 (SMD -2.9; 95% CI -4.8, -1.0; $p = 0.003$), and CA3 versus CA2 (SMD 0.7; 95% CI 0.3, 1.2; $p = 0.003$). No significant differences in neuronal loss were demonstrated comparing CA4 versus CA2 (SMD 0.4; 95% CI -0.5, 1.2; $p = 0.39$) and CA3 versus CA4 (SMD -0.2; 95% CI -1.2, 0.7; $p = 0.64$).

Separate measurement of hippocampal grey and white matter using 4.7 tesla MRI

Steve TA, Seres P, Huang Y, Wheatley M, Wilman A, Malykhin N, Gross DW
Supervisor: Dr. Donald W Gross

INTRODUCTION

Manual MRI-based volume measurements of the sub-regions of the hippocampus has the potential to improve diagnosis of several neuro-psychiatric disorders. Nearly all volumetry protocols presently in use include two white matter tracts, the alveus and the stratum lacunosum moleculare, in measurement of subfield volumes. Exclusion of these layers is likely to provide more anatomically accurate hippocampal volume measurements, and has recently been described using high-field MRI. We therefore aimed to determine if separation of grey and white matter structures of the hippocampus is possible using 4.7 tesla MRI and to assess the intra-rater reliability of this method.

METHODS

Six healthy control subjects were scanned at 4.7 tesla using a T2-weighted Fast Spin Echo (FSE) sequence (spatial resolution 0.52 X 0.68 X 1.0 mm). Segmentation was performed manually on inverted contrast images and repeated after a two-week interval for assessment of intra-rater reliability [calculation of intra-class correlation coefficients (ICCs) with a one-way fixed effects design].

RESULTS

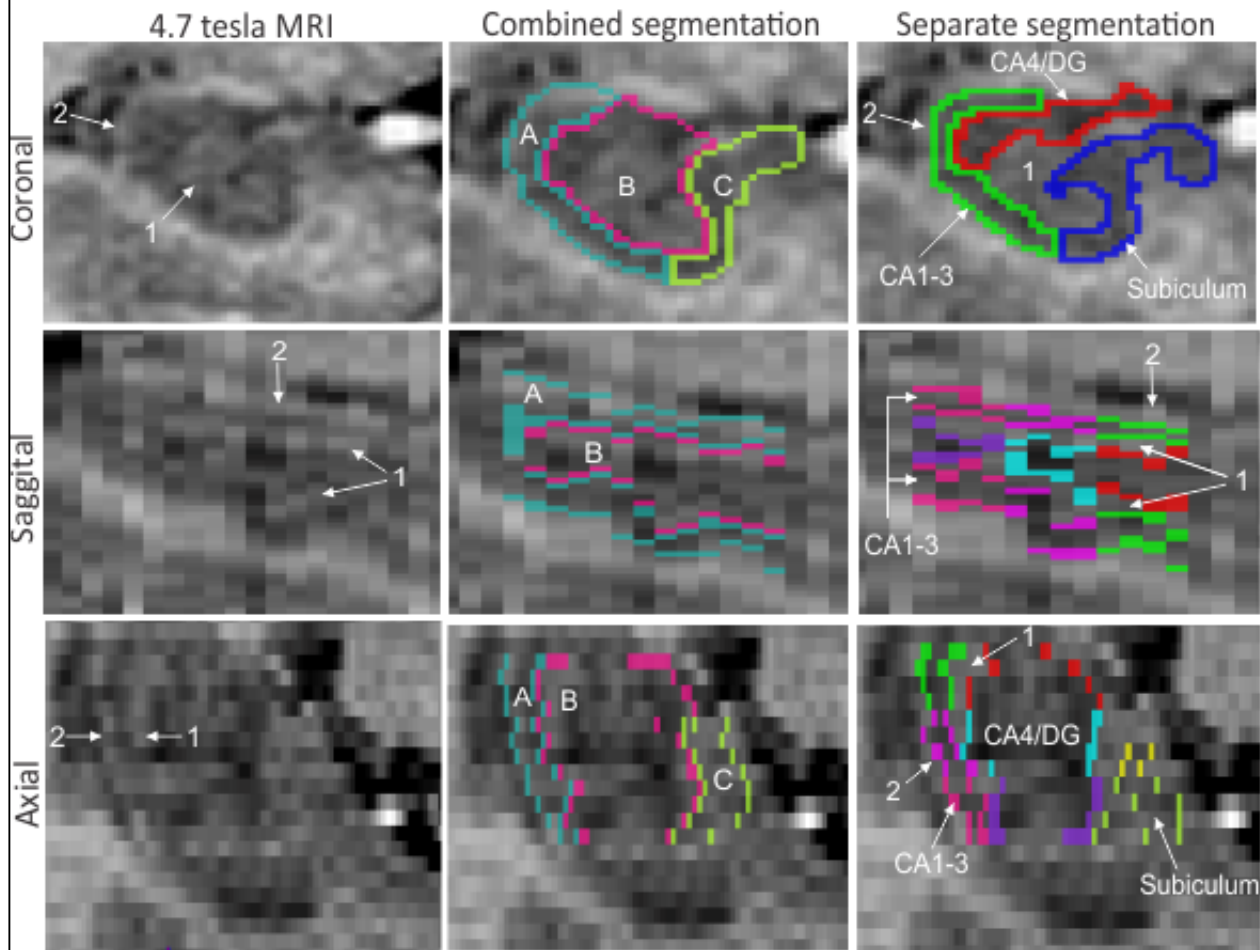
This study demonstrates feasibility of: i) Exclusion of the alveus from measurement of the CA1-3 subfields; and ii) Separation of the stratum lacunosum moleculare from measurement of the CA4/DG subfields. Intra-rater reliability (ICCs) for subfield volumes were as follows: Left CA4/DG (0.97), Right CA4/DG (0.88), Left CA1 (0.77), Right CA1 (0.84), Left Subiculum (0.70), Right Subiculum (0.80).

CONCLUSIONS

The present study demonstrates that separation of hippocampal grey and white matter is possible with 4.7 tesla MRI. Intra-rater reliability was comparable with that for previously described volumetry protocols. Use of this technique is likely to provide valuable information in neuro-psychiatric disorders such as Alzheimer's disease and epilepsy, which preferentially affect the hippocampal grey matter subfields.

Supervisor: Dr. Donald W Gross

Figure 1: Separation of hippocampal grey and white matter at 4.7 tesla



4.7 tesla MRI: Identification of the stratum lacunosum moleculare (1) and the alveus (2) in coronal, sagittal, and axial planes. **Combined segmentation:** Alveus is included in CA1-3 measurement (A). The stratum lacunosum moleculare is included in CA4/DG measurement (B). Measurement of the subiculum is also shown (C). **Separate segmentation:** The stratum lacunosum moleculare now forms the inferior boundary of CA4/DG (1). The Alveus forms the supero-lateral boundary of CA1-3 (2). **Subfield volumes (mm³, combined versus separate):** CA4/DG: 354.51 versus 210.65; CA1-3: 253.80 versus 207.22; Stratum lacunosum moleculare: 108.53 mm³ (not measured in previous protocol) **Abbreviations:** CA1-3: Cornu Ammonis 1-3; CA4/DG: Cornu Ammonis 4 / Dentate Gyrus

The Effect of IL-25 on Human Th2 Lymphocytes

Bredo G, Storie J, Palikhe NS, Davidson C, Adams A, Vliagoftis H and Cameron L
Supervisor: Dr. Lisa Cameron

INTRODUCTION

CRTh2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) is a marker for Th2 cells and activation through CRTh2 stimulates expression of cytokines important for allergic responses such as IL-4, IL-5 and IL-13. We have observed CRTh2+ T cells highly express the IL-25 receptor (IL-25R). IL-25 is produced by the epithelium in response to parasite, allergen, and virus, such as respiratory syncytial virus (RSV) possibly contributing to the initiation of Th2 immunity. In a mouse model where IL-25R signaling was deficient, CD4 T cells showed delayed Th2 differentiation. We hypothesize IL-25 modulates Th2 cell differentiation by directly acting on naïve human CD4 T cells.

METHODS

IL-25R expression was characterized using microarray, qRT-PCR and flow cytometry. The effect of IL-25 on Th2 differentiation was investigated by culturing naïve human CD4 T cells with α CD3/ α CD28 and IL-2 in Th2 conditions (IL-4, α IL-12 and α IFN γ) in the presence or absence of either IL-4, IL-25 or both. Proteins were detected by flow cytometry or ELISA. qRT-PCR was used to assay mRNA expression.

RESULTS

Microarray analysis showed that Th2 cells, compared to non polarized CD4 T cells are enriched in IL-25R mRNA (300 fold, $p < 0.05$), which was substantiated by qRT-PCR. IL-25 on its own induced Th2 differentiation as it increased expression of IL-4, GATA3 and CRTh2. Head to head comparison with the canonical Th2 cytokine, IL-4, showed that IL-25 was equally effective in inducing IL-4 ($p < 0.05$). IL-25 also increased expression of Th2 effector cytokines IL-5 and IL-13 ($p < 0.05$).

CONCLUSIONS

We observed that IL-25 (produced in response to pathogens such as RSV) can induce Th2 differentiation and the production of Th2 effector cytokines. Therefore, IL-25 inducing pathogens such as RSV may play a role in initiating and exacerbating allergic diseases.

Supervisor: Dr. Lisa Cameron

Rab32 Ties ER Stress to Apoptosis and Disrupts Mitochondria Functions within Neurons in vitro and Multiple Sclerosis Tissue

Xiaodan, Deng¹, Aleksandra, Janowicz², Michael, Bui², Paul, Eggleton⁴, Thomas, Simmen², Fabrizio, Giuliani^{1,3}
Supervisor: Dr. Fabrizio Giuliani

INTRODUCTION

Biopsies and post-mortem tissue of patients with multiple sclerosis (MS) as well as inflammatory demyelination animal models of MS show that endoplasmic reticulum (ER) stress is a hallmark of the progression of these pathologies. Moreover, MS biopsies and neuroinflammatory animal models have detected axonal damage associated with mitochondria fragmentation and impaired distribution as an early event in the absence of demyelination. It is thought that a combination of these phenomena makes cells more susceptible to inflammatory-mediated neurodegeneration and subsequent progression of the disease. Recent studies have demonstrated that Rab32, a small GTPase in the Ras protein family, plays a role in regulating mitochondrial mobility and ER stress induced apoptosis. Liang et al. showed that Rab32 expression sharply increases in response to acute brain inflammation, but subsequently drops. Based on the finding that activation of Rab32 induces ER stress related apoptosis and facilitates mitochondrial fragmentation via the activation of dynamin-related protein 1 (Drp1), we hypothesize that Rab32 could play a role in altering the axonal mitochondrial distribution and inducing neurodegeneration in MS.

METHODS

In this study, we probed and measured the levels of Rab32, ER stress and apoptosis related proteins in acute as well as chronic lesions and normal appearing white matter (NAWM) of inflamed MS brain tissues by Western blot and immunohistochemistry. Moreover, we examined mitochondrial morphology and distribution in human fetal neurons (HFN) transfected with Rab32 mutant plasmids and small hairpin RNA.

RESULTS

Indeed, we found that high levels of Rab32 coincide with ER stress-associated apoptosis in acute lesions and lead to shorter neurites with fragmented mitochondria in human neurons.

CONCLUSIONS

All findings are suggestive for a significant contribution of this protein in neurodegenerative progression of MS.

Supervisor: Dr. Fabrizio Giuliani

Transgenic mouse expressing a novel Gerstmann-Straussler-Scheinker disease Prnp allele with a partial duplication of the PrP hydrophobic domain.

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Supervisor: Dr. David Westaway

INTRODUCTION

Gerstmann-Straussler-Scheinker (GSS) disease is a rare, genetic prion disease that often manifests as progressive cerebellar ataxia and eventual cognitive decline. GSS can be distinguished from other prion diseases by the presence of widespread multicentric amyloid plaques containing prion protein fragments. Recently, a novel PRNP mutation was identified in a 34-year-old male. This allele codes for an 8 amino acid duplication of residues 122-129 (inserted between 129/130) extending the length of the hydrophobic domain (HD), the most highly conserved region of PrP. This expansion mutation is believed to have occurred *de novo*. We have created transgenic mice expressing the murine version of this allele and present biochemical and histopathological analysis of these animals as well as findings from cell culture models.

METHODS

Using independent lines of Tg mice expressing the mutant allele in the context of a valine codon at position 128 (human codon 129) we determined the age of onset of neurodegeneration and the transmissibility of the disease by intracranial inoculation. Histopathological analyses included immunostaining for PrP^{Sc}, assessment of vacuolation by H&E staining, determining the presence/extent of amyloid formation with Congo red and thioflavin S and immunostaining for glial fibrillary acidic protein (GFAP) to determine the extent of gliosis. We profiled PrP by immunoblot following exposure to PNGase F and proteinase K, and also assessed alternative membrane topologies of PrP (CtmPrP) arising from expansion of the hydrophobic domain. The susceptibility of cell culture models to stress-induction was analyzed for both mutant and control alleles.

RESULTS

Two independent Tg lines carrying the partial duplication of the HD ("Tg-Dupl" mice) developed a spontaneous neurologic syndrome at ages >300 days. This was associated with the accumulation of protease-resistant PrP fragments. Control Tg lines did not develop disease.

CONCLUSIONS

"Tg-Dupl" mice may comprise a new model for a variant form of human GSS.

Supervisor: Dr. David Westaway

Adaptation of prion-infected brain organotypic cultures to other species and brain regions.

J Campeau, G Norman, D McKenzie, V Sim
Supervisor: Dr. Valerie Sim

INTRODUCTION

The prion organotypic cerebellar slice culture assay (POSCA) is a powerful tool for the study of prion disease pathogenesis, as the model itself undergoes aspects of prion pathology, including loss of neurons and Purkinje cell dendritic spines. We have adapted POSCA to a cervidized mouse model and infected with chronic wasting disease (CWD). In addition, we have adapted it to non-cerebellar brain regions.

METHODS

Ten to twelve day old tga20 or tg33 mouse pups were used. Tga20 mice overexpress mouse PrPC by six times on a C57Bl6 background. Tg33 mice express wild-type deer PrPC on a mouse Prnp knockout background. 350 µm cerebellar slice cultures were prepared as described previously. For frontal cortex coronal sections, 250 µm sections were plated and infected. For rodent-adapted scrapie infections, slices were treated with 10 µg/mL brain homogenate from uninfected or infected terminally ill mice. For CWD infections, 100 or 1000 µg/ml of CWD from terminally ill wild-type deer was used. Infection was confirmed by immunoblotting for Proteinase K-resistant PrP using SAF83 (rodent-adapted scrapie) or Bar224 (CWD).

RESULTS

PK-resistant PrP is detectable at day 42 in coronal slices infected with rodent-adapted scrapie and at day 35 (1 mg/ml) and day 43 (100 µg/ml) in CWD infections. Levels increase over the duration of study (70 days). Interestingly, the banding profile of the replicated CWD PrP is distinct from the input PrPCWD.

CONCLUSIONS

We demonstrate that POSCA is a versatile technique not only suitable for rodent-adapted scrapie studies, but also for prion strains from other species. Additionally, we show that an adapted version of the POSCA technique can be used to study other brain regions to investigate the susceptibility of different brain regions to prion infection, removing the confounder of potentially different trafficking efficiency of prions to these brain regions in the brain in vivo.

Supervisor: Dr. Valerie Sim

Homology of TB fingerprint results on the Canadian Prairies: Implications for Programming

Heffernan, C; Varughese, B; Long, R; Gao, Z
Supervisor: Richard Long

INTRODUCTION

In connection with the Determinants of Tuberculosis Transmission (DTT) project, DNA fingerprint information of the disease causing agent, Mycobacterium tuberculosis, was collected for all culture positive cases of tuberculosis (TB) on the Prairies between July 1st, 2006 and December 31st, 2010 (n=1286). These molecular data were analyzed to determine homology of strains in Alberta, Saskatchewan and Manitoba.

METHODS

Isolates of M. tuberculosis were sent to the National Microbiology Lab (NML) in Winnipeg to be fingerprinted using Mycobacterial Interspersed Repetitive Unit (MIRU) typing. For this preliminary study, all results were compared on the basis of 12-loci MIRU. Most, but not all, isolates in our study period have 24-loci MIRU testing, which is more discriminatory and therefore adds specificity. SAS was used to find matches within provinces and across provincial borders – matches were determined by 100% congruence in the MIRU patterns of two or more isolates.

RESULTS

There were 385 unique fingerprints shared between the 1286 cases in the 4.5 year period. Alberta, in particular, had a high degree of uniqueness (80%) likely due to a large number of foreign-born cases, while few fingerprints were shared across the provinces. Manitoba had a low proportion of unique fingerprints (41%) likely attributable to data limitations or very large clusters in the province being shared with few cases outside of the province.

CONCLUSIONS

The trend in these descriptive data indicate that TB is a highly focal disease, though added discriminatory power in test methods may break down large clusters found within provinces. Transmission and clustering within a province of a particular strain is likely the result of environmental factors or gaps in TB programming rather than any hypothesized strain hyper-virulence. A related study will look at whether changes in less sensitive loci represent an evolutionary change in the bacteria rather than a different strain of TB.

Supervisor: Dr. Richard Long

Roles of insulin-like growth factor-II receptor and lysosomal enzymes in Alzheimer's disease pathology

Wang Y 1, 2, Westaway D 2, 3 and Kar S 1, 2, 3
Supervisor: Dr. Satyabrata Kar

INTRODUCTION

The insulin-like growth factor-II (IGF-II) receptor is an important regulator of lysosomal system involved in the transport of newly synthesized lysosomal enzymes from the trans-Golgi network to endosomes. Multiple lines of evidence have suggested that release of the lysosomal enzymes from lysosomes to cytosol and its activation can lead to neuronal death. Despite the fact that lysosomal system dysfunction has long been shown in Alzheimer's disease (AD) brains, little is known about functional interrelationship between the IGF-II receptor and lysosomal enzymes in the neurodegenerative process of AD. We hypothesize that release and activation of lysosomal enzymes can trigger neurodegeneration and possibly development of AD pathology.

METHODS

We used oligomeric human β -amyloid ($A\beta$)1-42-induced primary mouse cortical neuronal death model to evaluate the levels/activities and subcellular distributions of IGF-II receptor and lysosomal enzymes i.e. cathepsins B and D during neurodegeneration. In addition, we explored the neuronal death mechanisms using different cell death pathways. Ongoing experiments are also being carried out in the cortex of TgCRND8 and 5xFAD mouse models of AD.

RESULTS

We found levels of cathepsins B and D and to some extent the IGF-II receptor were increased with time during the oligomeric $A\beta$ 1-42-induced neuronal death. The increased cytosolic release of cathepsins B and D was associated with increased expression of pro-apoptotic molecular markers such as Bcl-2-associated X protein, cytosolic cytochrome c, cleaved caspase 3 and neuronal translocation of apoptosis inducing factor. In parallel, levels of cathepsins B/D and the IGF-II receptor were found increased in the cortex of TgCRND8 mice compared to age-matched control mice.

CONCLUSIONS

Cathepsin B/D and IGF-II receptor were increased in $A\beta$ 1-42-mediated neuronal death and the cortex of mice exhibiting AD-related pathology. Increased cytosolic release of cathepsin B/D may be associated with $A\beta$ 1-42-mediated neuronal death.

Supervisor: Dr. Satyabrata Kar

A randomized trial of the effect of pharmacist prescribing on improving blood pressure in the community: the Alberta clinical trial in optimizing hypertension (RxACTION) study

Ross T Tsuyuki, Sherilyn KD Houle, Theresa L Charrois, Michael R Kolber, Finlay A McAlister, Meagen M Rosenthal, Richard Lewanczuk, Dale Cooney

Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Since hypertension is largely managed through lifestyle and drug therapy, pharmacists can help address its management. In Alberta, some pharmacists are also authorized to prescribe. This study aimed to determine the effectiveness of pharmacist prescribing for patients with uncontrolled hypertension.

METHODS

Patients with undiagnosed or uncontrolled hypertension were randomized to enhanced care or usual care, with those randomized to enhanced care further randomized to either fee-for-service or pay-for-performance remuneration for the pharmacist. Enhanced care patients saw the pharmacist for blood pressure (BP) management including prescribing where appropriate for 6 months. Usual care patients had their BP measured at 3 and 6 months, but the pharmacist did not actively intervene with their care. The primary outcome was difference in change in systolic BP between the enhanced and usual care groups, with change in systolic BP between remuneration groups as a secondary outcome.

RESULTS

A total of 247 patients were enrolled in the study, with 180 randomized to enhanced care, and 67 to usual care. Within the enhanced care group, 91 patients were randomized to fee-for-service and 89 were randomized to pay-for-performance remuneration for the pharmacist. The required sample size of 340 patients was not achieved due to funding limitations. Systolic BP decreased by 17.9 mm Hg in the enhanced care group versus 11.0 mm Hg in usual care, resulting in a difference of 6.9 mm Hg (SE 2.3; $p=0.003$). Diastolic BP also differed between groups by 3.4 (SE 1.2) mm Hg, which was also significant ($p=0.005$). Due to inadequate sample size, the study was under-powered to detect a significant difference between remuneration groups.

CONCLUSIONS

This study, the first randomized trial of pharmacist prescribing, found that pharmacist care can lower systolic BP by 6.9 mm Hg more than usual care. Even with contamination between groups suspected, this represents a statistically and clinically significant improvement.

Supervisor: Dr. Ross Tsuyuki

Risk of hospital acquired diagnoses in patients with chronic kidney disease

Babak Bohlouli, Terri Jackson, Marcelo Toneli, Scott Klarenbach
Supervisor: Dr. Scott Klarenbach

INTRODUCTION

Unintended injuries, complications or diagnoses that arise during hospitalization are common and are associated with poor clinical and economic outcomes, and are of interest as they are potentially preventable. Identifying factors that increase the risk of developing hospital acquired diagnoses(HAD) may allow targeted prevention efforts. We sought to understand the association of CKD on the risk of developing a HAD.

METHODS

The cohort included all adults (age ≥ 18) residing in Alberta who were admitted to the hospital from March 31, 2003 to April 1, 2008, and the first hospitalization episode for each patient was considered. Subjects with end-stage renal disease (dialysis, transplant, eGFR <15) were excluded. Hospitalization for maternity/neonatal, congenital malformation, convalescence, and same day admission were excluded.

CKD was defined using pre-hospitalization outpatient eGFR and proteinuria, and co-morbid conditions were determined using validated algorithms on administrative data. HADs were defined by one or more diagnostic codes of conditions not present prior to hospitalization and arising during the hospitalization encounter. Logistic regression analysis was used accounting for available confounders.

RESULTS

In a cohort of 536549 subjects with hospitalization episodes, 45733 had CKD and 7.8% had one or more HAD. CKD of any severity was associated with increased risk of HADs of 1.22 (95% CI 1.11-1.28). Odds ratio of having HADs was reported 1.48(95% CI 1.42- 1.51) in episodes with the most severe CKD.

CONCLUSIONS

Pre-existing CKD has a graded association with the risk of developing HADs. Further inquiry into the nature of HADs and their preventability in subgroups of patients at high risk may improve patients outcomes and health care costs.

Supervisor: Dr. Scott Klarenbach

Table 2. Adjusted and unadjusted Odd ratio of having HADs

	adjusted HAD	P of CKD vs No CKD
Odd ratio of HADS	1.22	0.001
Odd ratio of HADS by primary code for hospitalization		
Certain infectious and parasitic disease	1.21	0.081
Neoplasm	1.15	0.001
Disease of blood and blood forming organs	1.29	0.133
Endocrine	1.3	0.001
mental behavioral	1.24	0.001
Disease of nervous system	1.36	0.001
Disease of eye	0.94	0.91
Disease of ear	2.28	0.168
Disease of circulatory system	1.19	0.001
Disease of respiratory system	1.23	0.001
Disease of digestive system	1.24	0.001
Disease of skin and subcutaneous	0.99	0.971
Disease of musculoskeletal system	1.13	0.001
Disease of genitourinary system	1.35	0.001
Symptom, signs of abnormal clinical and lab	1.35	0.001
Injury, poisoning	1.3	0.001

Table 3. Adjusted and unadjusted Odd ratio of having HADs

by CKD categories	Adjusted	p-value
> 60		
45 - 59	1.14	0.001
30 - 44	1.25	0.001
<29	1.48	0.001
by proteinuria level		
None		
Mild	1.65	0.001
Moderate	1.47	0.001
Heavy	1.61	0.001

Eight weeks of exercise training improves aerobic capacity, muscle mass, and fatigue in patients with Child Pugh class A and B cirrhosis - A randomized controlled pilot study

Laura Zenith, Neha Meena, Ailar Ramadi, Milad Yavari, Andrea Harvey, Michelle Carbonneau, Mang Ma, Juan G. Abraldes, Ian Paterson, Mark J. Haykowsky, Puneeta Tandon

Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Patients with cirrhosis have reduced exercise tolerance, measured objectively as decreased peak exercise oxygen uptake (peak VO₂). This is associated with decreased survival. The effect of aerobic exercise training (ET) on peak VO₂ has not been well studied in cirrhosis. We evaluated the safety and efficacy of 8 weeks of supervised ET on peak VO₂, quadriceps muscle thickness, and quality of life.

METHODS

19 clinically stable patients with Child Pugh class A or B cirrhosis were randomly assigned to ET or usual care(UC). Seventy-nine percent of patients were male with mean age of 57.6 ± 6.7 years and mean MELD score of 10 ± 2.2 . Supervised ET was performed on a cycle ergometer 3 days/week for 8 weeks at 60 to 80% of baseline peak VO₂. Peak VO₂, quadriceps muscle thickness (ultrasound), thigh circumference, Chronic Liver Disease Questionnaire(CLDQ), EQ-VAS, 6-minute walk distance, and MELD score were evaluated at baseline and 8 weeks. Statistical analysis was performed using ANCOVA.

RESULTS

Compared to UC, peak VO₂ improved by 5.3 ml/kg/min(95% CI: 2.9 to 7.8, $p=0.001$) after 8 weeks of ET. Thigh circumference ($p=0.001$), thigh muscle thickness ($p=0.01$), EQ-VAS determined self-perceived health status ($p=0.01$) and the fatigue subscore of the CLDQ ($p=0.01$) improved with ET. No adverse events occurred during cardiopulmonary exercise testing or training.

CONCLUSIONS

Eight weeks of supervised aerobic exercise training is a safe and effective therapy to improve peak VO₂, muscle mass and symptoms of fatigue in clinically stable patients with Child Pugh class A or B cirrhosis.

Supervisor: Dr. Puneeta Tandon

TRENDS OF BLEEDING AND TRANSFUSION AMONG PATIENTS WITH ACUTE CORONARY SYNDROME IN CANADA

Ghazi Alotaibi, M Sean McMurtry, Cynthia Wu, Padma Kaul
Supervisor: M Sean McMurtry

INTRODUCTION

Over the last decade, marked advances have been made in the diagnosis, treatment and prognosis of patients with acute coronary syndrome (ACS). We hypothesized that with this improvement in the rates of bleeding and blood transfusion were increased over time and both are associated with subsequent death and reinfarction.

METHODS

The Canadian Institute for Health information Database were used to determine all ACS indexed hospitalization from 2001, to 2009. Trends and rates of MB and blood transfusion (all comers) were analyzed to determine the annual and relative changes. Multivariate models were used to examine the association of MB and transfusion with reinfarction and in-hospital death.

RESULTS

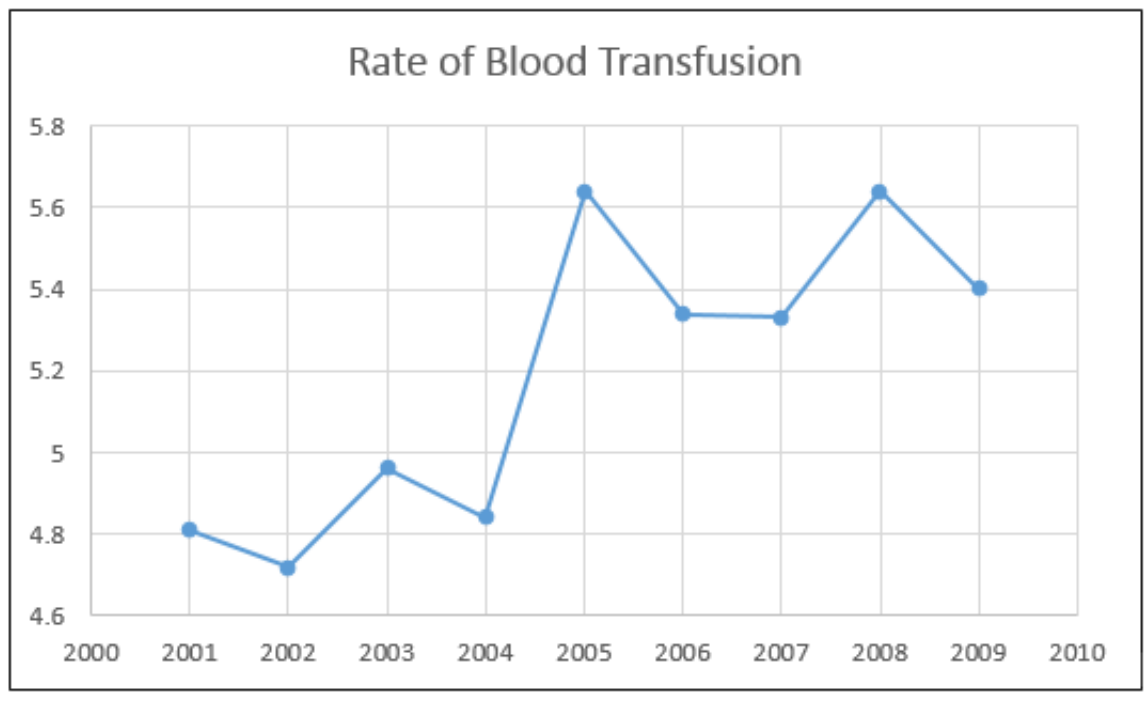
A total of 453,982 indexed hospitalizations were included. The incidence of major bleeding was 2.7% and the incidence of blood transfusion was 7.75 %. Standardized MB rate was 1.42 per 100 patients in 2001, and 1.14 per 100 patients in 2009. The rate of MB dropped significantly by 18.43% between the years 2001 and 2009 with a significant average annual reduction of 2.26%. The standardized blood transfusion rate was 4.81 per 100 patients in 2001, and 5.40 per 100 patients in 2009. Also, the relative rate of blood transfusion increased significantly by 17.3% between 2001 and 2009 with an overall annual increase of 2.23%. MB was associated with in-hospital mortality (adjusted OR 2.5, 95% CI: 2.36, 2.65) with no association with reinfarction (adjusted OR 1.06, 95% CI: 0.90, 1.26). Similarly, blood transfusion was associated with in-hospital mortality (adjusted OR 3.13, 95% CI: 2.98, 3.30) but not reinfarction (adjusted OR 0.91, 95% CI: 0.79, 1.05).

CONCLUSIONS

ACS patients have experienced a significant decline in MB events but a significant increase in transfusions . This finding is likely due to the use of more refined antithrombotics coupled with an increase in invasive therapies in high-risk patients and the accessibility of transfusion.

Supervisor: Dr. M Sean McMurtry

Figure 2: Rate of blood transfusion among non-CABG ACS patients (per 100 ACS patients).



A Community Based Approach to Dyslipidemia Management: Pharmacist Prescribing to Achieve Cholesterol Targets (RxACT Study)

Meagen Rosenthal; Dr. Glen Pearson; Dr. Ross Tsuyuki
Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Background: Dyslipidemia is an important modifiable risk factor for cardiovascular disease. Despite strong evidence and clear practice guidelines, it remains sub-optimally treated. Pharmacists are frontline primary care professionals, and, with expanded scopes of practice, could identify and treat patients with dyslipidemia.

Objective: To evaluate the effect of pharmacist prescribing and follow-up in patients with dyslipidemia not at recommended treatment targets.

METHODS

Methods: Design: Randomized trial of pharmacist prescribing vs. usual care.

Setting: Fourteen community pharmacies in Alberta.

Population: Adults with uncontrolled dyslipidemia (treated or untreated) as defined by the 2009 Canadian Dyslipidemia Guidelines.

Intervention: Pharmacists assessed patients' cardiovascular risk, reviewed LDL-c control, and developed treatment goals, including prescribing lipid-lowering medications. Follow-up was at 6, 12, 18 and 24 weeks.

Control: Patients received usual pharmacist and physician care, a copy of their lab results and a pamphlet on cardiovascular disease. Follow-up was at 12 and 24 weeks.

RESULTS

Results: We enrolled 99 patients with a mean (SD) age of 63 years (13), 49% male and mean baseline LDL-c 3.37 (0.98) mmol/L. The unadjusted proportion of patients achieving LDL-c target was 43% of intervention group, vs. 18% of controls ($X^2(1) = 7.24, p < 0.001$). This seems to represent the fact that based on the odds ratio, the odds of patients achieving target were 3.42 times higher if they were in the pharmacist intervention group. Intervention group subjects had a greater reduction in LDL-c (1.12 mmol/L, SD 1.09) vs. control (0.42 mmol/L, SD 0.66), $p < 0.01$.

CONCLUSIONS

Discussion: Pharmacist prescribing and follow-up in patients with dyslipidemia resulted in > 2-fold more patients achieving recommended target LDL-c levels. This could have major implications for prevention of cardiovascular disease in

Plasma Biomarker Analysis in Patients with Cardiomyopathy Secondary to Fabry Disease: Insight into the Pathophysiology of Fabry Cardiomyopathy

Brendan N. Putko, Haran Yogasundaram, Ian Paterson, Richard B. Thompson, and Gavin Y. Oudit

Supervisor: Dr. Gavin Oudit

INTRODUCTION

Fabry disease is an X-linked recessive lysosomal storage disorder with a global prevalence of 1 in 3000 individuals. Fabry disease is characterized by diminished or absent α -Galactosidase A activity, leading to the accumulation of globotriaosylceramide and cardiac, renal, and central nervous system dysfunction. Cardiomyopathy with diastolic dysfunction is the most common cause of death in patients with Fabry disease. Early detection is especially critical as progression of the disease can be halted by the initiation of enzyme-replacement therapy (ERT). Plasma biomarkers can provide prognostic and pathophysiological insights.

METHODS

Various biomarkers were studied in cohorts of Fabry disease (n=36) and gender-matched healthy controls (n=25). Enzyme-linked immunosorbent assays were used to investigate plasma levels of inflammatory markers tumour necrosis factor receptor 1 and 2 (TNFR1 and TNFR2), as well as markers of remodeling including brain natriuretic peptide (BNP) and mid-regional pro atrial natriuretic peptide (MR-proANP). Left ventricular hypertrophy (LVH) was assessed by cardiac magnetic resonance imaging. All subjects gave written informed consent.

RESULTS

Patients with Fabry disease had significantly elevated plasma levels of TNFR1 (1406 ± 1181 vs 937 ± 576 pg/mL, $p=0.04$), TNFR2 (1968 ± 867 vs 1235 ± 262 pg/mL, $p<0.001$), BNP (76 ± 87 vs 20 ± 18 pg/mL, $p=0.001$), and MR-proANP (101 ± 90 vs 51 ± 24 pM, $p=0.003$) relative to healthy controls. In addition, none of these biomarkers were significantly different in patients with concentric LVH relative to patients without LVH suggesting that they reflect systemic pathogenic alterations in these patients.

CONCLUSIONS

Inflammatory (TNFR1 and TNFR2) and remodeling (BNP and MR-proANP) biomarkers are elevated in patients with Fabry disease. The elevation of these biomarkers suggests that inflammation and myocardial remodeling are both important components of the heart disease in patients with Fabry disease. These features are consistent with a phenotype dominated by heart failure with preserved ejection fraction.

Supervisor: Dr. Gavin Oudit

Circulating levels of TNFR1 and TNFR2 are increased in HFPEF relative to HFREF: evidence for a divergence in pathophysiology

Brendan N. Putko, Zuocheng Wang, Jennifer Lo, Todd Anderson, Jason R. Dyck, Zamaneh Kassiri and Gavin Y. Oudit
Supervisor: Dr. Gavin Oudit

INTRODUCTION

Various pathways have been implicated in the pathogenesis of heart failure (HF) with preserved ejection fraction (HFPEF). Clinical trials in HFPEF of established therapies for HF with reduced ejection fraction (HFREF) have not been successful, which suggests that pathophysiological differences exist between HFPEF and HFREF. Inflammation induced by comorbid conditions, which are more prevalent in HFPEF, may play a proportionally larger role in driving HFPEF than HFREF.

METHODS

As part of the Alberta HEART project, the tumor necrosis factor-alpha (TNF α) axis was studied in community-based cohorts of HFPEF (n=100), HFREF (n=100) and healthy controls (n=50). Enzyme-linked immunosorbent assays were used to investigate levels of TNF α , its two receptors (TNFR1 and TNFR2), and a non-TNF α cytokine, interleukin-6 (IL-6) in plasma derived from peripheral blood. Blood sampling and echocardiography to grade diastolic function were performed during same-day enrolment. All subjects gave written informed consent.

RESULTS

More HFPEF patients were obese, hypertensive or diabetic, or had a history of smoking or atrial fibrillation (AFib) than HFREF patients. Plasma levels of TNF α and TNFR1 were significantly elevated in HFPEF relative to controls, while levels of TNFR2 were significantly higher in HFPEF than both controls and HFREF. TNF α , TNFR1 and TNFR2 were each significantly associated with at least three of the following co-variates: age, estimated glomerular filtration rate, hypertension, diabetes, smoking status or AFib in the combined HF cohort. TNFR2 levels were also significantly associated with severe diastolic dysfunction and HF symptoms in HFPEF.

CONCLUSIONS

Elevation of TNF α axis inflammation and a greater prevalence of comorbidities are characteristic of HFPEF. These findings and the observed association between inflammatory markers and comorbidities in HF suggests that inflammation mediated through the TNF α axis represents an important component of a comorbidity-induced inflammatory response that partially drives the pathophysiology of HFPEF.

Supervisor: Dr. Gavin Oudit

Left-atrial structural and functional remodeling in patients with different heart failure phenotypes: A cardiac MRI- and biomarker-based analysis

Brendan N. Putko, Richard B. Thompson, Ian D. Paterson and Gavin Y. Oudit
Supervisor: Dr. Gavin Oudit

INTRODUCTION

Atrial fibrillation (AFib), where the contractile function of the atrium is disrupted, is a significant risk factor for incident heart failure (HF) and is associated with more severe disease in patients with HF, particularly HF with preserved ejection fraction. Atrial contractility may be more important in HF patients whose stroke volume is not substantially reduced including mild HF with reduced ejection fraction.

METHODS

As part of the Alberta HEART project, we recruited healthy individuals (n=45) and community-dwelling patients with chronic heart failure (n=90) for cardiac MRI and mid-regional pro-A-type natriuretic peptide (MR-proANP) testing. We analyzed left atrial volumes (LAvols), indexed to body surface area, at three phases of the cardiac cycle: end systole (maximum LAvol), diastasis (intermediate LAvol) and end diastole (minimum LAvol). We calculated the following emptying volume indices (EVIs): passive (PEVI; maximum - intermediate LAvol), active (AEVI; intermediate - minimum LAvol) and total (TEVI; maximum - minimum LAvol). We plan to analyze ventricular volumes to determine atrial contributions to indexed stroke volumes.

RESULTS

Compared to controls, HF patients have significantly reduced PEVI and TEVI, but not AEVI. A subset of HF patients has no AEVI, while those with preserved atrial contractility exhibit an AEVI range similar to healthy controls. Advanced age and history of AFib are significantly associated with increases in indexed LAvols, while age is not associated with reduced AEVI, but history of AFib is. MR-proANP levels are significantly higher in HF than control, and are significantly associated with higher indexed LAvols.

CONCLUSIONS

In the context of significant increases in LAvols with both age and the presence of HF, patients whose atria have reduced elasticity, but preserved contractility might be high priority candidates for maintaining normal sinus rhythm. These results highlight the need for a personalized approach to rhythm versus rate control strategies in patients with incident AFib.

Supervisor: Dr. Gavin Oudit

TRAFFICKING OF CYTOKINES VIA RECYCLING ENDOSOMES IN NEUTROPHILS

Srivastava N, Hamburg R, Chesley A, Hum M and Lacy P
Supervisor: Dr. Paige Lacy

INTRODUCTION

Recycling endosomes (REs) are specialized secretory compartments that perform multiple functions. This study is focus on a little-known intracellular pathway involving recycling endosomes in cytokine trafficking in innate immune cells, and cytokine secretion is a fundamental mechanism in immunity. Neutrophils are highly abundant cells that are important in immediate responses to injury and infection, and secrete the proinflammatory cytokine TNF α . However, the trafficking and secretion of cytokines in neutrophils has not been characterized. Previous studies have shown that REs require the SNARE molecule VAMP-3 for trafficking to the cell surface. Our objective is to identify trafficking components in neutrophils that may contribute to cytokine secretion.

METHODS

Human peripheral blood neutrophils were adhered to glass slides and treated with bacterial lipopolysaccharide (LPS) for 30 min or 1 h (10 ng/ml). Cells were fixed and permeabilized before immunolabeling for intracellular TNF α . Anti-VAMP-3 and fluorescently labeled transferrin was used as RE markers to determine co-localization with TNF α . Imaging was carried out by Deltavision OMX superresolution microscopy. An ELISA was carried out on supernatants of LPS-stimulated neutrophils to confirm TNF α release.

RESULTS

Neutrophils possess REs as determined by transferrin uptake and VAMP-3 labeling. We found that TNF α immunoreactivity colocalized with VAMP-3 in LPS-stimulated neutrophils. We determined that co-localization of TNF α and VAMP-3 occurred around periphery of cells after 30 min and 1 h stimulation with LPS, suggesting release of cytokines at the cell membrane. TNF α release into supernatants of LPS-stimulated neutrophils occurred after 2 h.

CONCLUSIONS

The present study has provided evidence that LPS induces TNF α release, and that TNF α + vesicles co-localized with RE marker VAMP-3. Movement of TNF α +VAMP-3+ vesicles towards the cell periphery suggests that neutrophils utilize REs for trafficking of newly synthesized TNF α . These findings will contribute a new understanding of how innate immune cells package, transport, and release secretory products.

Supervisor: Dr. Paige Lacy

Three-Dimensional Method of Discs for Measurement of LV Volumes. Validation in a Dynamic Heart Phantom

Wood, P. W.; Gibson, P. H.; Becher, H.
Supervisor: Dr. Harald Becher

INTRODUCTION

Several methods are available to assess left ventricular (LV) volumes from a three-dimensional (3D) echocardiographic dataset, but these methods have not been compared in a heart phantom with good image quality. The currently established methods have all been reported to underestimate volume calculations. Therefore, we investigated the accuracy and reproducibility of LV volume measurements using a 3D method of discs (3D MOD) with manual tracing of multiple short axis areas.

METHODS

3D echocardiographic datasets were recorded in a dynamic heart phantom with an asymmetrical LV (apical aneurysm), using a commercially available scanner (IE33, Philips Inc.) and Q-lab software. Two independent readers measured LV volumes at multiple time points of the cardiac cycle using different methods of LV volume calculation (semi-automatic volume calculation - A1, with two manual correction methods - A2 and A3, Simpson's biplane - B, and 3D method of discs - C) comparing their results against the true volumes.

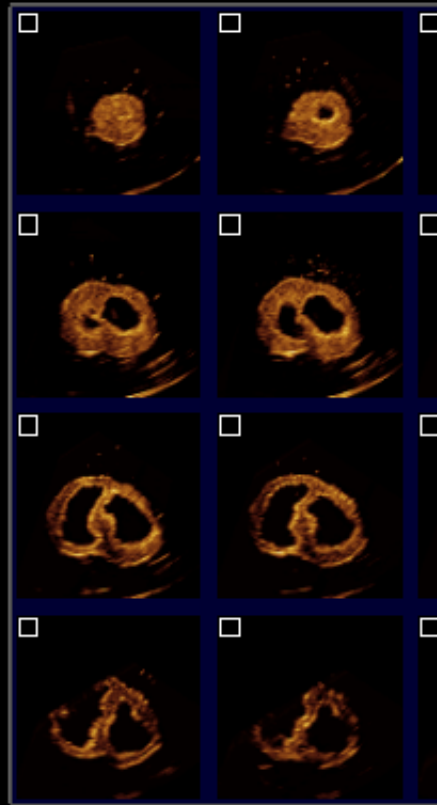
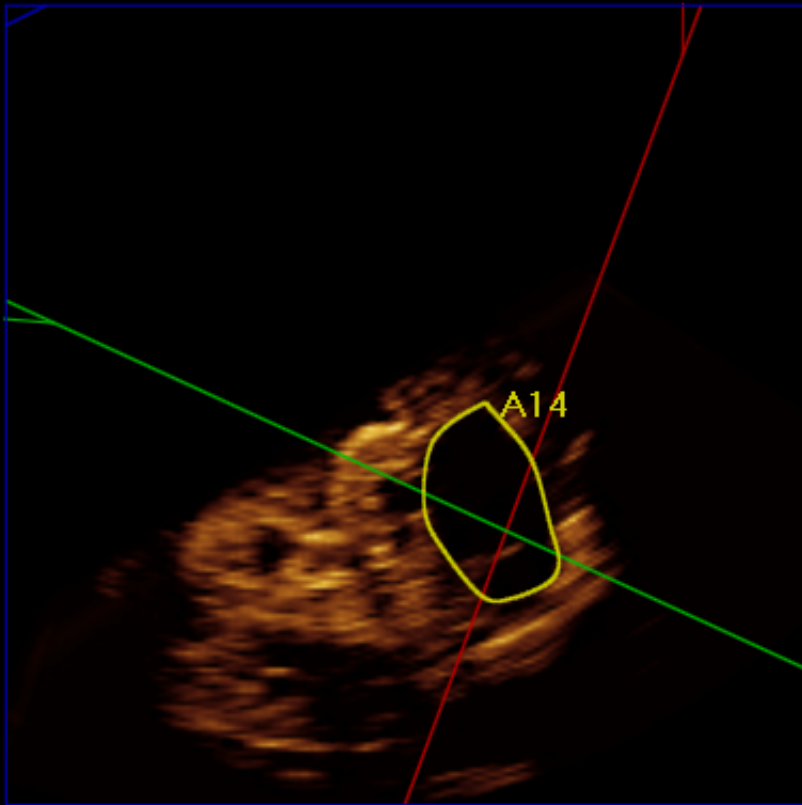
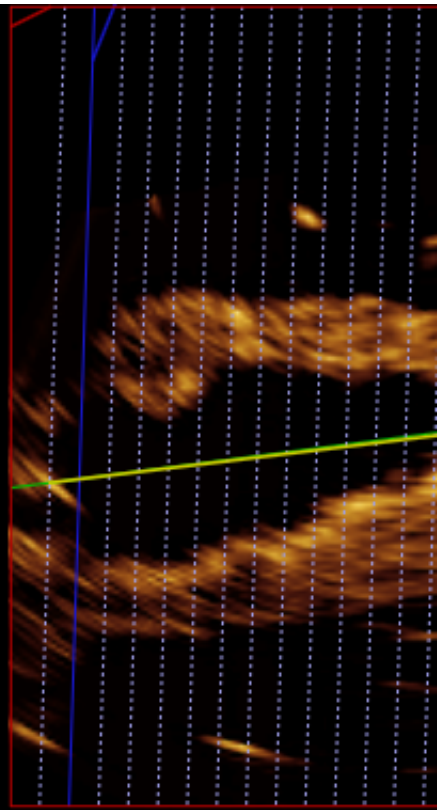
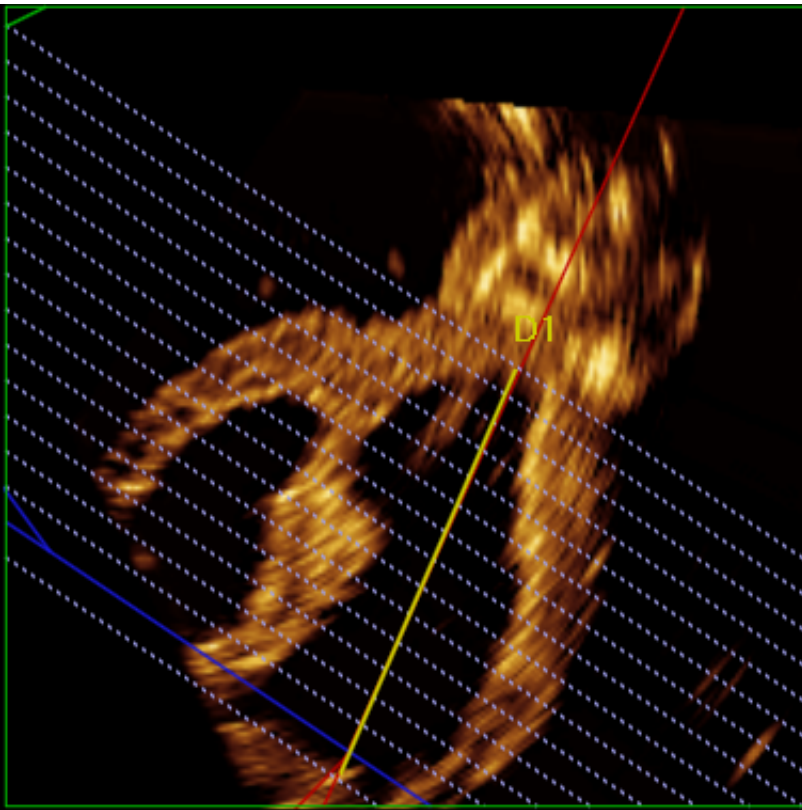
RESULTS

Compared to the true volumes method A1 resulted in an average underestimation of $16.5\% \pm 7.0$ with a good interobserver agreement (bias = 4.4 mL; LOA = 3.35 to 5.4mL). In methods A2 and A3 there was an average difference of $9.9\% \pm 7.3$ and $9\% \pm 7.8$ respectively; interobserver variability worsened (A2 bias = 6mL, LOA = -2.3 to 14.4mL; A3 bias 3.4mL; LOA = -9.8 to 16.7mL). Simpson's biplane had an average underestimation of $10.2\% \pm 8.0$. 3D MOD was the most accurate technique with an average underestimation of $3.5\% \pm 2.4$ and the best interobserver variability (bias = 0.9mL; limits of agreement -2.3 to 4.1mL).

CONCLUSIONS

In a heart phantom with good image quality the method of discs proved to be the most accurate and reproducible method of LV volume calculation. However, further development on semi-automated processing is needed in order to reduce the long time required for manual tracing.

Supervisor: Dr. Harald Becher



PHILIPS

Nuclear Pyruvate Dehydrogenase: A Novel Means of Epigenetic Regulation

Adam Kinnaird, Gopinath Sutendra, Roxane Paulin, Trevor Stenson, Peter Dromparis, Evangelos Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Nuclear DNA transcription, replication and repair are regulated by histone acetylation, where acetyl-transferases transfer the acetyl group from acetyl-CoA to conserved lysine residues. Acetyl-CoA is membrane impermeable and its biosynthesis occurs in the sub-cellular compartment it is required. Although the nuclear generation of acetyl-CoA is characterized in primitive eukaryotic cells, our knowledge in metazoan cells is limited. We hypothesized that the nucleus-encoded mitochondrial pyruvate dehydrogenase complex (PDC), which generates acetyl-CoA for the Krebs' cycle, is also present and functional in the nucleus of mammalian cells.

METHODS

We used several cancer and normal cell lines, in which we used mass spectroscopy, electron microscopy, confocal immunofluorescence and immunoblots in purified nuclear preparations (free of mitochondria).

RESULTS

We transfected cells with a plasmid encoding for pyruvate dehydrogenase in-frame with enhanced green fluorescent protein and detected its nuclear presence. Following isotope-labeled ¹³C from pyruvate to acetyl-CoA with mass spectrometry in isolated nuclei, we found that knockdown of nuclear PDC by small interfering RNA decreased the de-novo synthesis of acetyl-CoA in the nucleus. This also decreased acetylation of the core histones H2B, H3 and H4 and specific lysine residues 9, 18 and 56 of H3, required for cell cycle progression, in isolated nuclei exposed to pyruvate, resulting in decreased S-phase entry. PDC translocation to the nucleus was induced by EGF as well and inhibited by the EGF inhibitor, gefinitib. PDC immunoprecipitated with heat shock protein 70 (HSP70), a protein chaperone known to facilitate nuclear translocation. Inhibition of HSP70 prevented the increased nuclear localization of PDC induced by serum stimulation and EGF signaling.

CONCLUSIONS

We identified for the first time the nuclear presence of functional PDC. Nuclear PDC provides a mitochondria-independent pathway for acetyl-CoA synthesis, histone acetylation and cell cycle progression, offering a novel means of integrating cellular metabolism and epigenetic regulation of DNA.

Supervisor: Dr. Evangelos Michelakis

Inhibition of Pyruvate Dehydrogenase Kinase increases apoptosis and reduces proliferation and angiogenesis in Renal Cell Carcinoma

Adam Kinnaird, Peter Dromparis, Roxane Paulin, Gopinath Sutendra and Evangelos Michelakis

Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Renal Cell Carcinoma (RCC) exhibits a distinct metabolic phenotype known as the Warburg Effect. This principle describes cancer's preferential usage of cytoplasmic glycolysis (Gly) over mitochondrial glucose oxidation even in normoxia. Gly provides several growth advantages to cancer including increased angiogenesis and decreased apoptosis. The Pyruvate Dehydrogenase Kinase (PDK) inhibiting small molecule Dichloroacetate (DCA) decreases mitochondrial membrane potential ($\Delta\Psi_m$) and increases mitochondrial reactive oxygen species (mROS) in cancer cells thereby inducing apoptosis, inhibiting angiogenesis and tumor growth. The objective of this project is to assess the therapeutic effect of DCA for RCC.

METHODS

Two human kidney cell lines were used: (1) A proximal tubule (PT) epithelial cell line and (2) a clear cell RCC line. Cells were treated with 0.5 and 5mM DCA. Mitochondrial $\Delta\Psi_m$ and mROS were assessed using live cell imaging with TMRM and mitoxox, respectively. Tumor proliferation and apoptosis were measured using the markers ki67 and TUNEL, respectively. Nuclear localization of P53 was detected by immunofluorescence. PDH activity and α -ketoglutarate (α -KG) were measured using commercially available kits. Angiogenesis was assessed in-vitro by matrigel assay.

RESULTS

RCC cells have more hyperpolarized $\Delta\Psi_m$ ($p < 0.001$) and less mROS ($p < 0.001$) than PT cells. Treatment with DCA reversed these changes in the RCC line without significantly altering PT $\Delta\Psi_m$ or mROS. This is associated with a dose-responsive increase in PDH activity ($p < 0.05$) and increased levels of α -KG ($p < 0.01$). DCA increased nuclear localization of P53 ($p < 0.01$), which is associated with decreased markers of proliferation ($p < 0.05$), increased rates of apoptosis ($p < 0.01$), and a decreased rate of growth in vitro. The supernatant from RCC cells (containing angiogenic signals) increased vascularity, which was blocked by DCA treatment ($p < 0.05$).

CONCLUSIONS

DCA is an inexpensive, oral chemotherapeutic agent that reverses the mitochondrial remodeling of RCC. Treatment with DCA decreases proliferation and angiogenesis while increasing apoptosis in a human RCC line.

Supervisor: Dr. Evangelos Michelakis

CELLULAR IMMUNE RESPONSES TO HUMAN BETARETROVIRUS IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

Mandana Rahbari¹, Amir Landi², Michael Houghton² and Andrew Mason¹
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary biliary cirrhosis (PBC) is a destructive biliary disease characterized by anti-mitochondrial antibodies (AMA). A human betaretrovirus (HBRV) has been characterized in PBC patients that is associated with the aberrant expression of a protein resembling PDC-E2 in infected cells. We hypothesize that patients with PBC make cellular immune responses to PDC-E2 and HBRV.

METHODS

PBMC were purified from whole blood of 14 patients with PBC and 9 liver disease patients used for comparison. T-cell responses in peripheral blood mononuclear cells (PBMC) were assessed for reactivity to HBRV peptides and the characterized immunodominant 163-176 PDC-E2 peptide. PBMCs were stimulated with pools of overlapping 20-mer peptides from HBRV Envelope and Gag as well as PDC-E2. PHA-ionomycin mitogens and human cytomegalovirus Gag peptides were used as a positive control. The magnitude of Ex vivo responses to stimulation were evaluated by measuring production of IL12, IL-4, IL-10, TNF- α and IFN- γ assessed by FACS analysis to document T-cell memory responses.

RESULTS

Out of 14 patients with PBC, 4 showed memory CD8+ T-cell responses to HBRV Gag peptides, whereas none of 9 control samples showed reactivity to any of HBRV peptide pools ($P < 0.05$, one-sided Chi square). The magnitude of TNF- α and IFN- γ responses in memory CD8+ T-cell from PBC patients was significantly higher than that for the unstimulated cells; the range of responses varied from 1.25% to 4.97% to HBRV Gag peptides representing more than 8-36 fold increase. Out of 4 PBC patients that showed T-cell reactivity against HBRV Gag, 1 patient also showed memory CD8+ T-cell responses against HBRV Envelope (a sixfold response increase). None of PBC patients and control samples showed T-cell reactivity against PDC-E2 subunit peptides.

CONCLUSIONS

We found that 29% of patients showed reactivity to HBRV Gag pool of peptides. Further studies will be required to map the immunodominant HBRV Gag peptides to increase the sensitivity of the assay.

Supervisor: Dr. Andrew Mason

REGULATION OF PROTEINASE ACTIVATED RECEPTOR-2 (PAR-2) ON AIRWAY EPITHELIUM

Vivek Gandhi, Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Aeroallergens are major triggers of asthma. Many of these aeroallergens can activate PAR-2 receptors on the airway epithelium. We have shown that PAR-2 activation participates in allergic sensitization and allergic airway inflammation in animal models of asthma. Moreover, PAR-2 is upregulated on the airway epithelium of asthmatics, but the mechanisms and factors responsible are unknown. The asthmatic airways are under constant influence of inflammatory mediators and oxidative metabolism products. Furthermore inflammation causes tissue hypoxia and nutrient deficiency. Thus we hypothesized that the PAR-2 expression on the airways in asthma is regulated by cellular stress.

METHODS

To study the effect of cellular stress on PAR-2 expression, Normal Human Bronchial Epithelial cells were exposed to hypoxia, growth factor deprivation and oxidative stress for 24hrs/48hrs and PAR-2 mRNA levels were studied by qPCR. The effect of different growth media supplements such as epinephrine, hydrocortisone and retinoic acid on stress-induced PAR-2 was studied. PAR-2 function was assessed by measuring PAR-2-mediated IL-8 release.

RESULTS

Growth factor deprivation-induced stress upregulated PAR-2 mRNA (2.25 +/- 0.2 fold, n=6) in airway epithelial cells. Hypoxia and oxidative stress did not modulate PAR-2 expression (n=2). This stress induced PAR-2 upregulation was reversible after addition of growth factors (n=6) and was independent of any alterations in mRNA stability (n=3). Stressed cells showed upregulated PAR-2-mediated IL-8 release (2.1 +/- 0.2 fold, n=6) compared to the control cells. Addition of epinephrine reversed the effects of growth factors deprivation on PAR-2 expression (n=3).

CONCLUSIONS

Growth factor deprivation could be the driving force for PAR-2 upregulation in asthmatic airways. Activation of this upregulated PAR-2 can perpetuate inflammation by releasing higher levels of inflammatory mediators. Epinephrine, an adrenergic agonist, neutralizes stress effect on PAR-2 expression. Understanding PAR-2 regulation will allow us to devise approaches to decrease PAR-2 expression and prevent exacerbation of allergic airway inflammation.

Supervisor: Dr. Harissios Vliagoftis

Endothelial cell mTOR complex 2 regulates VEGF-induced sprouting angiogenesis in vitro and in vivo

Maikel Farhan¹, Katia Carmine-Simmen², John D Lewis², Ronald B Moore³, Allan G Murray¹

Supervisor: Dr. Allan Murray

INTRODUCTION

Vascular endothelial growth factor/-receptor (VEGF/VEGF-R) signaling mediates vascular development and re-vascularization of ischemic tissue. In the endothelium, VEGF/VEGF-R couples to phosphatidylinositol 3-kinase to signal to Akt1 and mammalian target of rapamycin complex-1 (mTORC1). The function(s) of endothelial mTORC2 positioned upstream of Akt and mTORC1 is poorly defined. We sought to investigate the role of mTORC2 in sprouting angiogenesis.

METHODS

We used pharmacological inhibitors and RNA interference to isolate function of mTORC2, Akt1, and mTORC1. Angiogenesis was evaluated in vitro and in vivo. To elucidate the mechanism of mTORC2-dependent events in angiogenesis, we studied migration, cytoskeleton reorganization, and focal adhesion formation in mTORC2-inactivated endothelial cells (ECs). We correlated these with candidate regulatory signaling events.

RESULTS

In primary human ECs, long-term, but not short-term, inactivation of mTORC1 activity paradoxically up-regulated Akt1 activation, that depended on mTORC2 activity. mTORC1/2 dual inhibition in vivo and mTORC2 inactivation in human ECs in vitro inhibited angiogenesis more effectively than mTORC1 inhibition alone. mTORC2-disrupted ECs migrated more slowly than Akt1- or mTORC1-deficient ECs. mTORC2 inactivation robustly suppressed VEGF-stimulated cytoskeleton reorganization of adherent EC. Further, mTORC2 inactivation perturbed EC focal adhesion formation, and activation of focal adhesion kinase, independent of Akt1.

CONCLUSIONS

Endothelial mTORC2 regulates angiogenesis by regulation of EC focal adhesion kinase activity, matrix adhesion, and cytoskeletal remodeling, independent of Akt/mTORC1.

Supervisor: Dr. Allan Murray

Metagenomics directed detection of African swine fever virus like sequences in the stool of IBD and PSC patients

Md Salman Reza, Weiwei Wang, Juan Jovel, Jordan Patterson, Glenn Ford, Eric Carpenter, Sandra O'Keefe, Tracy Jordan, Troy Mitchell, Andrew L. Mason, Gane Ka-Shu Wong

Supervisor: Dr. Gane Ka-Shu Wong, Dr. Andrew Mason

INTRODUCTION

Metagenomics sequencing is an emerging discipline to explore microbial diversity in clinical samples, independent of the limitations of cell-cultures. In this study, we used metagenomics sequencing to study diverse viral populations residing in patients with inflammatory bowel disease (IBD), in the hopes of finding novel viruses putatively associated with disease.

METHODS

Stool samples were collected from nine subjects with IBD, one primary sclerosing cholangitis (PSC) patient and two healthy controls. Viral enrichment of each homogenized sample was performed with glass-milk beads and by filtration. DNA and RNA were extracted from the viral preparations and used for making libraries with the Illumina TruSeq kit. After sequencing on the Illumina HiSeq or MiSeq platform, the sequenced data were assembled de novo and analyzed using bioinformatics search tools.

RESULTS

Assembly of 159,342,088 reads from 52 libraries generated using different viral enrichment methods resulted in 2,721,912 contigs or scaffolds. Sequence similarity search using blastn and blastx ended up with 503,058 annotated sequences from which viral sequences were identified. In our samples, fifteen mammalian viruses and sixteen plant viruses were found. The mammalian viruses included human picobirnavirus, African swine fever like virus (ASFV), herpesvirus, pox virus, human papillomavirus, circovirus and torque teno virus. Interestingly, we obtained the ASFV-like sequences showing thirty-nine genes hit along ASFV genome. However, the translated amino acid sequences shared identity of only 38-62% with ASFV proteins in the database. In addition, phylogenetic analysis indicated the position of ASFV-like sequences in a clade different from that of ASFV in terms of topoisomerase, capsid and 220 KDa polyprotein.

CONCLUSIONS

We are reporting for the first time the presence of African swine fever virus like sequences in human clinical samples in North America. The amino acid variation with ASFV proteins and phylogenetic analysis indicate that our sequences could be a new member of Asfarviridae family to which ASFV belongs.

Supervisor: Dr. Gane Ka-Shu Wong, Dr. Andrew Mason

Predicted Weight Loss Required by the Severely Obese to Achieve Clinically Important Differences in Health-Related Quality of Life

Lindsey M. Warkentin (1,2) , Sumit R. Majumdar (1,2) , Jeffrey A. Johnson (2,3), Raj S. Padwal (1,2)

Supervisor: Raj Padwal

INTRODUCTION

Guidelines suggest that 5-10% reductions in body weight are clinically important. It is not clear if these thresholds correspond to improvements in health-related quality of life (HRQL). In a prospective study at a the Edmonton Weight Wise clinic, we evaluated the 2-year change in HRQL in wait-listed, medically managed, and surgically treated severely obese patients, to predict the threshold of weight loss needed produce minimal clinically important differences (MCIDs) in HRQL.

METHODS

Two-year changes in Short-Form (SF)-12 Physical (PCS) and Mental (MCS) component summaries, EQ-5D Index and Visual Analog Scale (VAS), and Impact of Weight on Quality of Life (IWQOL)-Lite total score were calculated. Multivariable linear regression models were constructed to determine the association between weight loss and HRQL. Model coefficients were used to estimate the weight reductions required to achieve the pre-defined MCID for each HRQL instrument.

RESULTS

Mean age was 43.7 (SD 9.6) years, 88% were women, 92% were white, and mean initial BMI 47.9 (SD 8.1) kg/m². In surgically-treated patients (2-year weight loss = 16%), mean improvements in HRQL were greater than the MCID thresholds for all scores except the MCS, compared to wait-listed. In medically-managed patients (2-year weight loss = 3%), only mean improvements in EQ-index were greater than the MCID, compared to wait-listed. Percent weight reductions to achieve pre-defined MCID were: 23% (95% CI: 17.5, 32.5) for PCS, 25% (17.5, 40.2) for MCS, 9% (6.2, 15.0) for EQ-Index, 23% (17.3, 36.1) for EQ-VAS, and 17% (14.1, 20.4) for IWQOL-Lite total score.

CONCLUSIONS

Weight reductions to achieve MCID for most HRQL instruments are markedly higher than the conventional threshold of 5-10% reductions. Weight loss achieved with surgical-treatment, but not medical-management, consistently led to clinically important improvements in HRQL over 2-years in severely obese patients receiving in a publicly funded bariatric care.

Supervisor: Dr. Raj Padwal

High Dose Vitamin D Supplementation Stimulates Innate Cytokine Responses in Patients with Inflammatory Bowel Disease on Infliximab

Krista M. Reich, Karen Madsen, PhD, Rae R. Foshaug, Richard N Fedorak, MD, Karen I. Kroeker, MD

Supervisor: Dr. Karen Kroeker

INTRODUCTION

Vitamin D deficiency is highly prevalent among patients with inflammatory bowel disease (IBD). In that vitamin D is an important immunomodulator of both the innate and adaptive immune system, it has been suggested that vitamin D deficiency may have a role in the development of IBD as well as influencing disease severity. Therefore, understanding the impact of vitamin D supplementation on the inflammatory cytokine cascade in IBD patients will be critical for improving clinical care of these patients.

METHODS

Adult Crohn's disease and ulcerative colitis patients on maintenance (q8w) infliximab therapy were invited to participate. Serum vitamin D and cytokine (IL-1 β , IL-2, IL-8, IL-12, GM-CSF, IFN- γ , IL-6, IL-10, and TNF- α) levels were measured immediately before the infliximab infusion. Vitamin D deficient patients (serum 25(OH)D levels <75 nmol/L) were then administered a high dose (250,000-500,000 IU) of vitamin D intramuscularly within 2 weeks following their infusion. Vitamin D sufficient patients were not supplemented. Measurements of serum vitamin D and cytokine levels were repeated 8 weeks later just prior to their next infusion.

RESULTS

Twenty patients in stable clinical remission were recruited. At baseline, 8/20 (40%) patients were vitamin D deficient. There were no significant differences in mean baseline cytokine levels between the groups (data not shown). However, after vitamin D supplementation, serum levels of IL-1 β , IL-6, GM-CSF, and IL-8 significantly increased in the supplemented vitamin D deficient group compared to the non-supplemented group (Table 1). Comparison of the cytokine levels in the supplemented vitamin D deficient group showed a significant increase in IL-1 β , IL-6, GM-CSF, and IL-8, with no difference in IL-2, IL-12, IFN- γ , IL-10, or TNF- α levels post supplementation (data not shown).

CONCLUSIONS

The increase in IL-1 β , IL-6, GM-CSF, and IL-8 following vitamin D supplementation in vitamin D deficient IBD patients supports a role for vitamin D as a stimulator of the innate immune response.

Supervisor: Dr. Karen Kroeker

Table 1. Cytokine levels at follow up, stratified by vitamin D group

Cytokine	Cytokine levels in the vitamin D sufficient group at follow up (pg/ml) (n=12)	Cytokine levels in the vitamin D Deficient Group (After Supplementation) (pg/ml) (n=8)	P-value
IL-1 β Median (IQR)	0.16 (0.01-0.28)	0.82 (0.37-4.30)	0.007
IL-2 Median (IQR)	0.39 (0.12-0.52)	0.49 (0.31-1.18)	0.31
IL-8 Median (IQR)	19.3 (9.70-26.56)	71.2 (20.92-192.59)	0.031
IL-12 Median (IQR)	0.97 (0.55-1.98)	1.05 (0.68-1.60)	1.00
GM-CSF Median (IQR)	0.09 (0.00-0.37)	0.44 (0.25-2.85)	0.047
IFN- γ Median (IQR)	3.01 (1.41-4.70)	3.08 (1.12-6.24)	0.97
IL-6 Median (IQR)	1.74 (1.05-2.12)	3.32 (2.02-28.58)	0.02
IL-10 Median (IQR)	2.86 (1.90-3.82)	3.92 (2.35-4.49)	0.38
TNF- α Median (IQR)	9.80 (6.28-11.86)	9.72 (8.36-10.97)	0.68

DEMOGRAPHIC AND GEOGRAPHICAL CHARACTERISTICS OF TUBERCULOSIS TRANSMISSION IN THE ABORIGINAL PEOPLES OF ALBERTA AND SASKATCHEWAN

Patel, S., Long, R., Saunders, D. L., Heffernan, C
Supervisor: Dr. Richard Long

INTRODUCTION

The Aboriginal peoples of Canada account for >50% of all Canadian-born TB cases. Of these groups, the Registered Indian and Métis peoples in the provinces of Alberta, Saskatchewan and Manitoba (i.e the 'Canadian Prairies') contribute more than one-half of all Aboriginal cases in Canada. This study aims to describe the demography and the community of residence of adult (>14 years) Registered Indian and the Métis peoples diagnosed with culture-positive pulmonary TB (PTB) and their contacts who were tuberculin Skin Test (TST) converters in Alberta and Saskatchewan in 2007 and 2008. Transmission events of these cases were defined as tuberculin skin test (TST) converters that were or were not secondary cases.

METHODS

The transmission events were identified using conventional (contact tracing) and molecular (genotyping of Mycobacterium tuberculosis isolates with Mycobacterium Interspersed Repetitive Units) methods. A descriptive study was undertaken to characterize all transmission events by age, gender, population group, and community type.

RESULTS

A total of 104 Aboriginal PTB cases were diagnosed in the study period; 73 (70%) Registered Indian and 31 (30%) Métis. Their mean age was 38.2 years (SD =16.7); 50(48%) were male; and 56(54%), 24 (23%), and 24(23%) resided in reserve communities, Métis settlements, and metropolitan areas, respectively. Of the 104 PTB cases, 48 had 464 contacts and no converters and 56 (38 Registered Indian; 18 Métis) had 1729 contacts and 187 converters. Of all converters, 51 (27.3%) were secondary cases. The mean age of secondary cases was 20.6 years (SD= 18.1); 29 (57%) were male; and 32 (62.7%), 11 (21.6%), 8(15.7%) were situated in reserve communities, Métis settlements and metropolitan areas, respectively.

CONCLUSIONS

TB transmission in Alberta and Saskatchewan is reported in over half of the Aboriginal cases with the potential to transmit. TST converters that were secondary cases were largely confined to the community of residence of the potential source case.

Supervisor: Dr. Richard Long

Table 1.Characteristics of tuberculin skin test converters identified from 104 Aboriginal pulmonary TB cases in Alberta and Saskatchewan: 2007-2008

Characteristics	Alberta	Saskatchewan	Total	χ^2 ; P-value*
No. of TST converters	44	143	187	
Disease status				
Culture-positive secondary case	8	34	32(17.1%)	
Culture-negative secondary case	3	16	19(10.2%)	
Absence of disease	33	103	136(72.7%)	
Age				
0 to 15	14	82	96(51.3%)	$\chi^2=11.2$; P=0.004
15 to 34	14	38	52(27.8%)	
≥ 35	16	23	39(20.9%)	
Total	44	143	187	
Population Group				
Registered Indian	26	117	143(76.5%)	$\chi^2=51.6$; P<0.001
Métis	1	22	23(12.3%)	
Canadian-born Aboriginal	2	3	5(2.7%)	
Unknown	15	1	16(8.6%)	
Gender of Secondary cases (n=51)				
Male	5	24	29(56.9%)	$\chi^2=0.74$; P=0.388
Female	6	16	22(43.1%)	
Total	11	40	51	
Community of Residence of Secondary case (n=51)				
on-reserve	7	25	32(62.7%)	P=0.037**
Métis settlement	0	11	11(21.6%)	
Metropolitan	4	4	8(15.7%)	
* Pearson's Chi-Squared test was conducted for all categories greater than 5 counts				
**P-value corresponds to a one-tailed Fisher's Exact test				

Impaired axonal integrity of corpus callosum in acute phase predicts persistent cognitive deficits in Transient ischemic attack and minor ischemic stroke patients at 90 days.

Mahesh P Kate, Leka Sivakumar, Laura Gioia, Parnian Riaz, Thomas Jeerakathil, Brian Buck, Richard Camicioli, Christian Beaulieu, Kenneth Butcher
Supervisor: Kenneth Butcher

INTRODUCTION

Persistent cognitive deficits (PCD) are present in significant proportion of patients with transient ischemic attack and minor ischemic stroke (TIA/MIS). The pathological mechanisms of PCD in this group of patients have been poorly elucidated. We hypothesize; patients with persistent CD at 90 days after TIA/MIS would have reduced fractional anisotropy (FA) in normal appearing white matter (NAWM) tracts.

METHODS

Twenty-five acute TIA/MIS patients (NIH stroke scale ≤ 3) without history of dementia were prospectively enrolled within 48 hours of symptom onset. Montreal cognitive assessment (MoCA) was administered at baseline 7, 30 and 90 days. Magnetic resonance imaging (MRI) of brain including diffusion tensor imaging (DTI) was performed at 7 and 30 days after symptom onset. Raw DTI images were post-processed to generate FA map and diffusion-weighted images (DWI) (b values 0 s/mm² and 1000 s/mm²). White matter tracts were then assessed with Region-of-interest (ROI) analysis after appropriate masking of white matter hyperintensity (WMH) and acute infarcted tissue. Independent ROI analysis and tractography was performed by threshold propagation method for projection, association and commissural fibers (Table 1).

RESULTS

Fifty-two percent (13/25) and 28 % (7/25) patients had baseline and 90 days cognitive impairment (MoCA ≤ 26). Baseline DWI volume [Median (IQR) 0.9(3.28)] ml was not a predictor of PCD ($p=0.79$). Moderate to severe WMH was present in 36% (9/25). The mean (SD) FA in NAWM tracts at 7 and 30 days in patients with PCD was 0.46(0.01) and 0.47(0.02) respectively vs. without PCD 0.49(0.02) ($\beta = 0.94$, $p=0.03$) and 0.49(0.01) ($p=0.07$). The mean (SD) FA in corpus callosum at 7 and 30 days in patients with PCD was 0.55(0.04) and 0.55(0.06) respectively and without PCD 0.62(0.04) ($\beta=0.94$, $p=0.001$) and 0.62(0.03) ($\beta=1.1$, $p=0.004$).

CONCLUSIONS

In acute TIA/MIS patients' impaired axonal integrity of NAWM tracts particularly the corpus callosum and not baseline infarct volume is a predictor of persistent CD.

Supervisor: Dr. Kenneth Butcher

Table 1: Mean Fractional anisotropy (FA) in region-of-interest in white matter areas at 7 days and 30 days

	FA at 7 days	FA at 30 days	Correlation	p value
Right PLIC	0.57±0.03	0.55±0.02	0.32	0.11
Left PLIC	0.56±0.03	0.54±0.04	0.31	0.21
Right Cingulum	0.54±0.04	0.54±0.04	-0.63	0.95
Left Cingulum	0.56±0.05	0.55±0.06	0.63*	0.19
Right ARC	0.37±0.05	0.38±0.05	0.73*	0.22
Left ARC	0.37±0.05	0.35±0.05	0.71*	0.04
Right SRC	0.46±0.04	0.47±0.04	0.66*	0.84
Left SRC	0.45±0.05	0.45±0.05	0.77*	0.62
Fornix	0.37±0.07	0.36±0.05	0.19	0.22
Genu of CC	0.57±0.07	0.57±0.06	0.83*	0.58
Splenium of CC	0.64±0.05	0.64±0.05	0.78*	0.9
Right SLF	0.47±0.05	0.45±0.05	0.66*	0.05
Left SLF	0.45±0.05	0.44±0.05	0.66*	0.66
NAWM tracts	0.48±0.03	0.48±0.02	0.66*	1
Infarct tissue	0.26±0.09	0.24±0.1	0.87*	0.28
PV WMH	0.3±0.09	0.29±0.04	0.69*	0.71
DWM WMH	0.33±0.07	0.32±0.05	0.42*	0.63

*PLIC- Posterior limb of internal capsule, ARC- anterior region of the internal capsule, SRC-superior region of internal capsule, CC-corpus callosum, SLF- superior longitudinal fasciculus, NAWM-normal appearing white matter, PV WMH- periventricular white matter hyperintensity, DWM WMH- deep white matter white matter hyperintensity. * Significant correlation*

Reduction of PrPC and Shadoo proteins during prion infection as a host protective response

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Supervisor: David Westaway

INTRODUCTION

Prion diseases are a group of incurable neurodegenerative disorders that affect several mammalian species including bovine spongiform encephalopathy in cattle and Creutzfeldt-Jakob disease in humans. During prion infections, the cellular prion protein (PrPC) is converted into a misfolded form (PrPSc), which is the only known component of the infectious prion particle. Our laboratory has recently shown that the accumulation of PrPSc parallels a significant preclinical reduction in PrPC and PrP-like Shadoo (Sho) glycoprotein levels. Since PrPC is a substrate required for PrPSc synthesis and toxic signaling, our data support the hypothesis that a protective host response is responsible for the slowly evolving pathogenesis that characterizes many natural prion diseases.

METHODS

Assuming a common underlying mechanism for reductions in PrPC and Sho, we have used newly-developed in vitro and ex vivo models for Sho downregulation in conjunction with chemical inhibitors to define the of protein quality control systems involved in this effect. Analyses were performed at the molecular and microscopic levels.

RESULTS

Sho exhibits a robust response to proteasomal inhibition, thus indicating a potential relationship between this quality control system and downregulation events in the adult brain.

CONCLUSIONS

Drugs that enhance this natural protective PrPC downregulation response may be beneficial in treating prion disease.

Supervisor: Dr. David Westaway

Depression and obesity severity, using a clinical obesity staging system

Ayodele A. Ogunleye (PhD)^a, Denise Campbell-Scherer (MD)^b, Christian Rueda-Clausen (MD)^c, Rajdeep Padwal (MD)^c, Arya M. Sharma (MD)^a
Supervisor: Dr. Arya Sharma

INTRODUCTION

Introduction:

There is evidence that severe obesity is associated with depression, but there has been no study that has used a more clinically meaningful measure of obesity severity. Using the Alberta population-based prospective evaluation of the quality of life outcomes and economic impact of bariatric surgery (APPLES) data, we aim to evaluate the relationship between obesity severity and depression.

METHODS

Methods:

This analysis includes baseline data from 500 individuals recruited into the three arms of the APPLES (waiting list, medical treatment, surgical treatment). Obesity severity was defined using the Edmonton Obesity Staging System (EOSS), a 5 point ordinal scale (0–4), which ranks severity of obesity based on the presence of risk factors, comorbidities and end-organ damage. For this study, stage 4 was collapsed into stage 3 due to low numbers ($n=1$). History of depression was either self-reported or based on drug treatment. Using logistic regression models, controlling for age, sex, education, marital status, ethnicity, cigarette smoking, diabetes, and obesity arm of treatment, we compared risks of depression in obese individuals categorized in different EOSS obesity severity stages.

RESULTS

Results:

Overall, 60% of our sample had a history of depression. When compared with EOSS stage 0, the adjusted odds ratio (OR) of depression for individuals in EOSS stage 1 was 3.75 (95%CI=1.54 to 8.98), for stage 2 was 4.52 (95%CI=2.06 to 9.91) and for stage 3-4 was 4.93 (95%CI= 1.71 to 14.22). Obese females were almost three times more likely to have history of depressed than males (OR= 2.81, 95%CI= 1.52 to 5.18).

CONCLUSIONS

Conclusions:

These findings suggest that increasing severity of obesity is associated with an increased likelihood of having a history of depression. This is particularly true in women. Further research into the role of depression in the aetiology and management of obesity appears warranted.

Supervisor: Dr. Arya Sharma

Title: Intracerebral hemorrhage volumes, but not blood pressure reduction are correlated with small amounts of perihematoma ischemia.

Laura C. Gioia, Mahesh P Kate, Victor Choi, Derek Emery, Ken Butcher.
Supervisor: Dr. Ken Butcher

INTRODUCTION

Background: Diffusion-weighted imaging (DWI) studies have identified ischemic tissue both in and outside the perihematoma (PH) region in ICH patients. We aimed to identify the frequency of DWI lesions, measured objectively using Apparent Diffusion Coefficient (ADC) thresholds. We tested the hypotheses that larger ICH volumes and blood pressure (BP) reduction are correlated with PH and remote ischemia.

METHODS

Methods: We conducted a retrospective analysis of 100 ICH patients who underwent DWI. ICH and PH volumes were measured planimetrically. PH regions with low ADC values were identified using thresholds for moderate ($<730 \times 10^{-6} \text{mm}^2/\text{s}$) and severe ($<550 \times 10^{-6} \text{mm}^2/\text{s}$) ischemia. Weighted average BP over the first 24h after onset (24hBP) and low SBP load (fraction of time spent $<150 \text{mmHg}$) were calculated.

RESULTS

Results: The median (IQR) time to MRI was 2(5) days. Median ICH volume was 13.8(27.7) ml. Median PH edema volume was 12.1(23.8) ml, with a mean ADC value of $1099.4 \pm 180.3 \times 10^{-6} \text{mm}^2/\text{s}$. A small portion of the PH region contained tissue reaching moderate (0.07(0.11))% or severe ischemic ADC thresholds (0.002(0.003))%. The volume of tissue reaching both ADC thresholds correlated with ICH volumes (moderate: $R=0.568$, $p<0.001$, severe: $R=0.523$, $p<0.001$), but not 24hBP ($R=0.05$, $p=0.6$, and $R=0.02$, $p=0.86$) or low SBP load ($R=0.34$, $p=0.73$, and $R=0.06$, $p=0.67$), respectively. DWI lesions remote from the PH region were found in 19(19%) patients. Mean PH ADC values were similar in patients with ($1093.5 \pm 177 \times 10^{-6} \text{mm}^2/\text{s}$) and without remote DWI lesions ($1100.8 \pm 182.1 \times 10^{-6} \text{mm}^2/\text{s}$, $p=0.70$). Patients with and without DWI lesions had similar 24hBP (144.7 ± 14.7 vs. 142.7 ± 20.0 , $p=0.58$) and low SBP load ($55.5 \pm 35.4\%$ vs. $59.5 \pm 36.1\%$, $p=0.82$, respectively).

CONCLUSIONS

Conclusion: The PH region contains primarily elevated ADC values, consistent with vasogenic edema. Small volumes of PH ischemia are correlated with larger ICH volumes, but BP reduction is not associated with remote or PH DWI lesions.

Supervisor: Dr. Ken Butcher

CRTh2+Th2 cells are increased in severe asthma and resistant to steroid intake

Shrestha Palikhe N, Lane C, Nahirney D, Vethanayagam, D, Vliagoftis H, Cameron L

Supervisor: Dr. Lisa Cameron

INTRODUCTION

Chemoattractant receptor homologous molecule expressed on Th2 cells (CRTh2) is expressed by Th2 cells, eosinophils and basophils. It is a receptor for PGD2 and plays an important role in allergic inflammation. We assessed the abundance of CRTh2-expressing cells between different asthma phenotypes and examined steroids effect on Th2 cells.

METHODS

Asthmatics were recruited from the outpatient tertiary referral center at the University of Alberta. Severe asthma was defined by ATS guidelines. The proportion of leukocytes expressing CRTh2 was determined in whole blood by flow cytometry. Expression of CRTh2 was measured by qPCR. Serum IL-13 and PGD2 levels were measured by ELISA. SNP genotyping was performed for CRTh2 -6373G>A. Steroid responsiveness of CRTh2-expressing cells was assessed using in-vitro differentiated Th2 cells.

RESULTS

Severe asthmatics exhibited a higher % of circulating CRTh2+ Th2 cells ($p<0.01$), CRTh2 mRNA expression and serum IL13 ($p<0.05$) compared to mild/moderate asthmatics. There was no difference in the % of eosinophils expressing CRTh2 between the two asthma phenotypes. Patients having more than ≥ 1 urgent care visit (UCV) had higher serum PGD2 ($p<0.01$) and higher PGD2 group showed higher CRTh2 -6373GA+AA compared to GG genotype ($p<0.05$). Severe asthmatics having ≥ 1 UCV had more CRTh2+ Th2 cells compared to mild/moderate asthmatics ($p<0.01$). Culturing human Th2 cells in the presence of dexamethasone showed no change in the Th2 cell viability and CRTh2 expression, unlike the soluble mediators IL-13.

CONCLUSIONS

These finding indicate that more CRTh2+Th2 cells in severe asthma may be due to steroid resistance of Th2 cells and might be the reason why they persist in-vivo and associates with exacerbation. PGD2 associates with asthma exacerbation and CRTh2 genetic polymorphism, which further suggests involvement of PGD2 mediated pathway. Our findings identify CRTh2 as a possible therapeutic target for decreasing pulmonary inflammation and interrupting the Th2 immune cascade in severe asthmatics.

Supervisor: Dr. Lisa Cameron

The Design of the Alberta Vascular Risk Reduction Community Pharmacy Project: Rx EACH

Ross Tsuyuki, Brenda Hemmelgarn, Charlotte Jones, Dunsı Oladele, Yazid N Al Hamarneh
Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Risk factors for vascular disease remain poorly identified and treated.

Objective: To evaluate the effect of a community pharmacy-based case finding and intervention program on reduction in cardiovascular risk.

METHODS

Design: Randomized controlled trial

Setting: 70 community pharmacies in Alberta.

Patients: 1180 adults at high risk for cardiovascular events (including high risk primary prevention, established vascular disease, chronic kidney disease and/or diabetes) identified by the pharmacist.

Intervention: The pharmacist will conduct a structured medication review, including patient assessment, laboratory tests (HbA1c, lipid panel, creatinine, urine albumin), individual cardiovascular risk assessment and education regarding this risk. Pharmacists will prescribe, adapt, or recommend medications as necessary to achieve targets for lipids, smoking cessation, glycemic control and hypertension. Follow-up is every 4 weeks for 3 months.

Control: Usual care by the pharmacist and physician with no specific intervention for 3 months. After that, patients are crossed-over to receive the intervention described above and followed for another 3 months

RESULTS

Primary outcome: Difference in change in cardiovascular risk between intervention and control groups. Cardiovascular risk is defined as the risk for future cardiovascular events (myocardial infarction, revascularization, cardiovascular death) as estimated by validated risk engines (Framingham, International, and UKPDS).

CONCLUSIONS

This is the first large scale randomized trial on global cardiovascular risk reduction in a community pharmacy setting. It utilizes the community pharmacists' expanded scope of practice and the existing remuneration system in Alberta. Rx EACH is a unique collaboration between Alberta Health, Alberta Health Services, University of Alberta, University of Calgary and industry.

Supervisor: Dr. Ross Tsuyuki

The Validity of Home Blood Pressure Monitor Validation Studies

Sherilyn KD Houle, Yazid N Al Hamarneh, Ross T Tsuyuki
Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Recent guidelines highlight the importance of home blood pressure monitoring. Although “validation” studies of home monitors have been published, the quality of their methods has not been evaluated.

Objective: To perform a systematic review of the published peer-reviewed literature on the validity of home blood pressure monitors and to assess their adherence to validation standards.

METHODS

We searched MEDLINE, Embase, Cochrane Library, and CINAHL to April 2013. Studies were included if they claimed to evaluate the accuracy/validity of upper arm home blood pressure monitors, and were excluded if conducted only in special populations (pregnancy, kidney disease, etc.) or using wrist or finger devices. Study methods were compared to the validation protocol(s) referred to in the article (e.g., British Hypertension Society) or, if not specified, to protocols existing at the time of publication.

RESULTS

4473 studies were identified; 97 met our inclusion criteria. Across all included studies, 93% reported comparing the test device with manual readings, 80% had a sufficient sample size, 79% utilized two trained observers, 68% took an adequate number of measurements per subject, 67% took measurements following the proper sequence, and only 15% described enrolling subjects of sufficient variability (age, systolic and diastolic BP, and arm circumference).

CONCLUSIONS

None of the reviewed studies claiming to validate home blood pressure monitors fully adhered to the validation standards. This may lead to both false-positive (claims that the device is accurate) and false-negative claims. When interpreting the findings of validation studies, pharmacists should critically evaluate their adherence to accepted validation standards.

Supervisor: Dr. Ross Tsuyuki

GENERATION AND UTILIZATION OF HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS-DERIVED-IPS FOR STUDYING ENDOTHELIAL GENE REGULATION

Nakhaei-Nejad M, Murray A.G. and Jahroudi N.
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Damage to endothelial cells (EC) of blood vessels is the core of various vascular diseases. The mechanism that establishes EC phenotype is not known. Induced pluripotent stem cells (iPS) provide a valuable in vitro system to study the molecular processes, including EC-specific gene regulation, that contribute to establishment of EC phenotype. We aimed to study endothelial gene regulation by generating iPS from human umbilical vein EC (HUVECs) and differentiating the resulting iPS back into EC. This model provides a system with a homogenous genetic background to explore how EC phenotype is revoked (HUVEC to iPS), and reestablished (iPS to EC).

METHODS

iPS colonies were generated using originally reported transcription factors. Quantitative RT-PCR and immunofluorescence analysis were used to characterize iPS and cell lineages derived from iPS. Pluripotency of the iPS were demonstrated by generation of embryoid bodies (EB) and detection of the three germ layer markers, as well as direct differentiation to their lineages including neurons, cardiomyocytes, as well as EC.

RESULTS

We explored the mechanism of activation and repression of a highly EC-specific gene, von Willebrand factor (VWF), in HUVEC, iPS, EB and iPS that was differentiated into EC (EC-diff). We explored whether the expression pattern of transcription factors that regulate VWF are associated with establishment of EC phenotype. Transacting factors that participate as repressors of VWF promoter were increased in iPS and EB compared to HUVEC and EC-diff, while those functioning as activators were undetectable in iPS and EB but detected to similar levels in HUVEC and EC-diff. Temporal expression of activators were observed during various stages of differentiation. Furthermore, the ability of iPS to incorporate into microvasculature was demonstrated in a mouse model of kidney vascular injury.

CONCLUSIONS

This system provides an opportunity for understanding endothelial gene regulation and consequently enables us to develop new therapeutic approaches for vascular diseases.

Supervisor: Dr. Nadia Jahroudi

Distinct microRNA profiling in the Right and Left Ventricle of Patients with Dilated Cardiomyopathy and its regulation by LVAD implantation

Ratnadeep Basu^{1,4}, Nirmal Parajuli^{1,4}, Konrad S. Famulski², Daniel Kim^{1,4}, John Mullen^{4,5}, Holger Buchholz³, Philip F. Halloran² and Gavin Y. Oudit^{1,4}
Supervisor: Gavin Y. Oudit

INTRODUCTION

Dilated cardiomyopathy (DCM) involves progressive myocardial dysfunction and is a leading indication for cardiac transplantation. Left ventricular assist device (LVAD) has emerged as a tool to maintain tissue perfusion in patients either waiting or ineligible for heart transplantation. Non-coding micro RNA (miRNA) impacts myocardial remodeling by negatively regulating the gene mRNA expression.

METHODS

We investigated, the role miRNA in the myocardial reverse remodeling in patients with end-stage DCM. Right (RV) and left (LV) ventricle free wall tissue from explanted (n=16) and non failing control (NFC, n=6) human hearts were collected with the aid of HELP and HOPE program respectively. Global miRNA expression profiling was performed in DCM patients with (n=8) and without (n=8) an LVAD and compared to NFC, using the miRNA 3.0 Array chip. The groups of miRNA involved in the diseases process was evaluated and corresponding genes were identified using the Ingenuity Pathway Analysis (IPA) program.

RESULTS

In the failing LV, a total of 41 miRNA's were expressed in patients with LVAD as oppose to 20 miRNA's without LVADs, compared to the NFC group. Interestingly 14 miRNA were co-expressed in both the LVAD and no LVAD groups and 6 miRNAs were reversed. In contrast, 170 miRNA's were expressed in the RV in patients without LVADs and the majority of these (n=165) were reversed in response to LVAD therapy. These miRNAs are key regulators of the pathological signaling and hypertrophy and likely represents key drivers of the reverse remodeling in the LV and RV.

CONCLUSIONS

LVAD regulates the expression of miRNA in both the RV and LV in a chamber-specific manner. The differential reversal of miRNA expression is profound in the RV, indicating an active genetic induction of reverse remodeling of the RV in patients with LVAD.

Supervisor: Dr. Gavin Y. Oudit

Infliximab trough level is correlated with Infliximab-associated adverse events in IBD patients

Huang, V; Dhami, N; Prosser, C; Shalapay, C; Kroeker, KI; Dhami, Neil; Fedorak, Darryl K; Fedorak, Richard N
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Infliximab is an effective therapy in the management of inflammatory bowel disease (IBD). Infliximab-associated adverse events (IAAE) including skin rashes, arthralgias, neuropathy and infusion reactions are frequently reported. The relationship of IAAEs to serum levels of infliximab has not been evaluated. The aim of this study was to determine the prevalence of IAAEs in IBD patients and evaluate their relationship to infliximab trough levels (ITL).

METHODS

In this cross-sectional study, consecutive IBD patients were recruited from the University of Alberta IBD infliximab infusion clinic between 2012 and 2013. The patient's medical records were reviewed for IAAEs (skin rashes, arthralgias, neuropathy, and infusion reactions). Each IAAE required documentation by two patient self-reports and/or a physician report. ITL were obtained immediately before the infliximab infusion and measured using an in-house ELISA assay. Results are presented as median ITL (IQR). Differences in median ITL were analyzed using non-parametric Mann-Whitney or Kruskal Wallis tests.

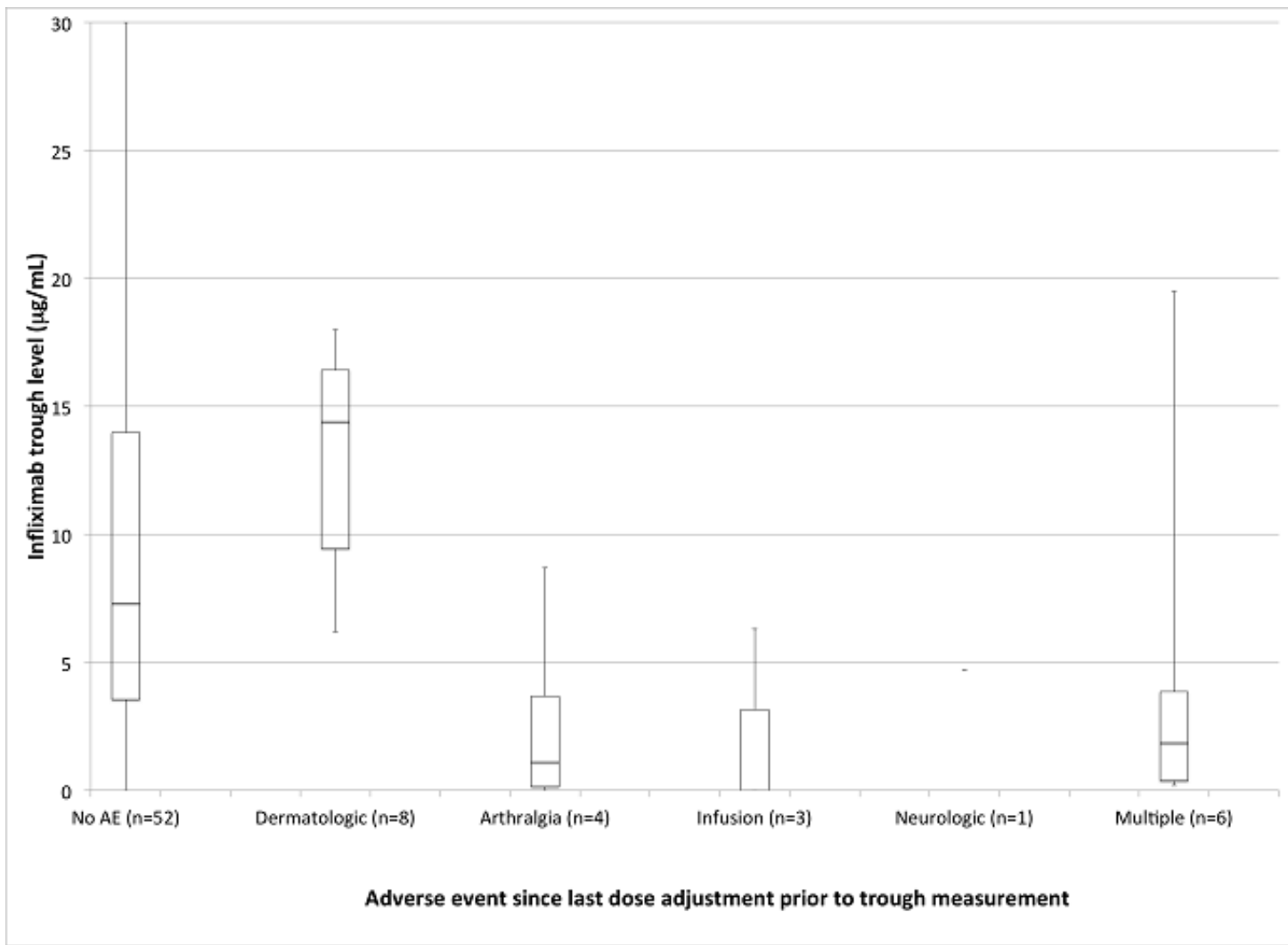
RESULTS

74/87 patients had records that permitted complete documentation of any IAAEs. 36/74 (48.6%) had IAAEs at any time during their infliximab history, while 22 (29.7%) had IAAEs reported since the last dose adjustment prior the ITL. More females than males reported IAAEs (66.7% vs. 33.3%, $p=0.015$), otherwise there were no demographic variables associated with IAAEs. As shown in Figure 1, the median ITL was higher in patients who reported dermatological IAAEs compared to those who reported arthralgias, infusion reactions, neuropathies, or multiple IAAEs.

CONCLUSIONS

Nearly half of IBD patients on infliximab report infliximab associated adverse events. A low infliximab trough level was associated with infusion reactions, while a high infliximab trough level was associated with dermatological adverse events. This disparity suggests that infliximab associated adverse events may have different pathological mechanisms.

Supervisor: Dr. Richard Fedorak



Left Ventricular Assisted Device (LVAD) Reverses Adverse Myocardial Remodeling in the Right and Left Ventricle in Patients with Dilated Cardiomyopathy

Nirmal Parajuli^{1,4}, Ratnadeep Basu^{1,4}, Konrad S. Famulski², Daniel Kim^{1,4}, John Mullen^{4,5}, Holger Buchholz³, Philip F. Halloran² and Gavin Y. Oudit^{1,4}

Supervisor: Gavin Y Oudit

INTRODUCTION

Heart Failure (HF) continues to be a common cause of morbidity and mortality on a world-wide basis and dilated cardiomyopathy (DCM) represents an important cause of HF. LVAD therapy has emerged as a mode of therapy for advanced HF by unloading the LV and maintaining systemic perfusion.

METHODS

Right (RV) and left (LV) ventricle tissue from explanted failing and non-failing control (NFC) human hearts were collected via the HELP and HOPE programs, respectively. Global mRNA expression profiling in DCM patients without (n=8; 7M/1F; age range: 42-54 yrs; ejection fraction (EF): 17.5 % (15-26%) and with (n=8; 7M/1F; age range: 44-58 yrs; EF 15% (12.5-25.0%) LVAD (HeartMate II) was compared to NFC (n=6; 4M/2F) as control. mRNA microarray was done using Affymetrix prime view gene chips and evaluated using the Ingenuity Pathway Analysis (IPA) program.

RESULTS

LVAD use was associated with marked reverse remodeling of the LV and RV with reduced myocardial hypertrophy and interstitial fibrosis based on standard histological assessment. Total gene entities of 991 in the LV and 860 in the RV were reversed in hearts with DCM without LVAD. LVAD use was independently associated with the regulation of 280 genes in the LV and 380 genes in the RV. The total upregulated/downregulated genes involved in cardiac hypertrophy ranged from 15 to 30% and fibrosis ranged from 10 to 50% were reversed in both the RV and LV in response to LVAD therapy. In addition, 30-50% of the total apoptotic-related genes and 10-30% of the cytokine-related genes were also reversed in both the RV and LV.

CONCLUSIONS

LVAD reduced pathological hypertrophy and fibrosis in both LV and RV and is correlated with altered gene expression controlling cardiac hypertrophy and myocardial fibrosis, and apoptotic and inflammatory pathways. LVAD therapy represents a viable long-term therapy for HF patients.

Supervisor: Dr. Gavin Y Oudit

Angiotensin converting enzyme 2 deficiency results in cardiac insulin resistance in response to high-fat diet

Vaibhav B. Patel^{1,2}, Jun Mori^{2,3}, Brent A McLean^{2,4}, Gary D. Lopaschuk^{2,3}, Gavin Y. Oudit^{1,2,4}

Supervisor: Dr. Gavin Oudit

INTRODUCTION

Activation of the renin-angiotensin system can alter the cardiac energy substrate preference, thereby contributing to the progression of heart failure. Angiotensin converting enzyme (ACE) 2 is a key negative regulator of the renin-angiotensin system where it metabolizes angiotensin (Ang) II into Ang 1-7. Obesity is a major risk factor for type 2 diabetes and cardiovascular diseases. We studied the role of ACE2 in high-fat diet (obesity) induced diabetic cardiomyopathy and heart disease.

METHODS

ACE2-null (ACE2^{-/-}; ACE2KO) mice and wildtype (WT) litter-mate controls were fed with high-fat diet (HFD; 45 kcal%) or control diet (10 kcal%) and studied at 6-month of age.

RESULTS

ACE2KO-HFD mice showed increased fasting plasma glucose along with equivalent increase in the total fat and cardiac hypertrophy compared with WT-HFD mice. We subjected hearts to ex vivo aerobic perfusions to measure cardiac function and rates of cardiac energy metabolism. HFD-fed ACE2KO mice showed markedly decreased cardiac work along with blunted insulin response on glucose as well as palmitate oxidation suggesting increased insulin resistance, a precursor of the metabolic syndrome, in the ACE2KO-HFD mice. ACE2KO-HFD hearts relied almost exclusively on fat metabolism as the energy source, a feature observed in cardiomyopathy associated with obesity and type II diabetes. Metabolic changes in the ACE2KO-HFD were associated with impaired insulin signaling (decreased p-Akt) and decreased p-AMPK. ACE2KO-HFD hearts showed increased phosphorylation of pyruvate dehydrogenase, the rate-limiting enzyme of carbohydrate oxidation, which leads to deactivation of the enzyme.

CONCLUSIONS

Renin-angiotensin system plays an important role in cardiac metabolism. We found a novel role of ACE2 in cardiac insulin signaling, where ACE2 negatively regulates obesity and hyperglycemia induced cardiac insulin-resistance and alterations in cardiac metabolism. Enhancing ACE2 action may have therapeutic effects against obesity and diabetes induced heart disease.

Supervisor: Dr. Gavin Oudit

Angiotensin converting enzyme 2 is a critical determinant of angiotensin II-induced loss of vascular smooth muscle cells and adverse vascular remodeling

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Supervisor: Dr. Gavin Oudit

INTRODUCTION

Angiotensin converting enzyme (ACE) 2 is a key negative regulator of the renin-angiotensin system (RAS) and metabolizes angiotensin (Ang) II into Ang 1-7. Ang II is a vasoactive peptide which plays an important role in vascular disease. The objective of present was to define the role of ACE2 in pathological vascular remodeling.

METHODS

ACE2 knockout (ACE2KO) and wildtype (WT) litter-mate controls were subjected to Ang II-infusion for 2 or 4 weeks.

RESULTS

We found upregulation of ACE2 in dilated human aorta with bicuspid aortic valve (BAV) and in murine aorta in response to Ang II. Ex vivo pressure myography showed increased vascular stiffness in ACE2KO mesenteric arteries (MA) in response to Ang II (1.5 mg/kg/day) and with aging. Histological analyses revealed reduced media-to-lumen ratio in ACE2KO MA with loss of vascular smooth muscle cells (VSMCs). Aortic VSMCs from ACE2KO mice showed markedly increased reactive oxygen species (ROS) and apoptosis in response to Ang II along with increased cleaved caspase-3 and cleaved caspase-8 levels in the ACE2KO aorta. AT1 receptor blockade and Ang 1-7 supplementation prevented the increase in Ang II-induced ROS and apoptotic cell death. In the aorta, Ang II resulted in thoracic and abdominal aortic dilation with loss of VSMC density in ACE2KO aorta as revealed by α -smooth muscle actin, calponin staining and electron microscopy with increased pro-matrix metalloproteinase (MMP) 2, MMP2 and MMP9 levels. ACE2 is upregulated in vascular diseases and ACE2 deficiency exacerbates Ang II-mediated vascular remodeling driven by increased ROS and VSMC apoptosis.

CONCLUSIONS

In conclusion, the key counter-regulatory role of ACE2 against an activated RAS provides novel insights into the role of ACE2 in vascular diseases.

Supervisor: Dr. Gavin Oudit

Insight into the metabolic basis of pulmonary hypertension: the role of the mitochondrial deacetylase Sirt3.

Roxane Paulin, Peter Dromparis, Gopinath Sutendra, Adam Kinnaird, Sotirios Zervopoulos, Alois Haromy and Evangelos D. Michelakis.
Supervisor: Dr Evangelos D. Michelakis

INTRODUCTION

Similar to cancer, suppression of mitochondrial function promoting proliferation and apoptosis-resistance has been described in the pulmonary arteries and extra-pulmonary tissues in Pulmonary Arterial Hypertension (PAH), a deadly disease. Although its reversal by metabolic modulators holds therapeutic promise, the cause of this metabolic remodeling is unknown. Sirtuin 3 (Sirt3), is a mitochondria-localized deacetylase that regulates mitochondrial function. Loss of Sirt3 activity promotes acetylation and inhibition of many mitochondrial enzymes and electron transport chain complexes, resulting in an overall mitochondrial suppression. Sirt3KO mice develop spontaneous cancer and loss-of-function polymorphisms in the SIRT3 gene have been associated with metabolic abnormalities in affected patients. We hypothesized that loss of SIRT3 promotes PAH.

METHODS

We used WT and KO Sirt3 mice as well as monocrotaline (MCT)-induced PAH in rats. In vitro, we used PSMCs isolated from WT and KO Sirt3 mice. We also used human PSMCs, Buffy Coats (n=152) and transplant tissues (n=10) from normal or PAH patients.

RESULTS

Sirt3KO mice developed spontaneous PAH exhibiting previously described features of the PAH vasculature (mitochondrial hyperpolarization, STAT3, NFATc2 and HIF-1 α activation, proliferation and resistance to apoptosis). In the MCT rat model, SIRT3 was downregulated and intra-tracheal nebulization of Sirt3 adenovirus at day 21-post MCT injection, improved pulmonary pressures and vascular remodeling compared to the GFP-only adenovirus treated rats. In human PAH cells and tissues SIRT3 expression was also decreased. More importantly, we found that a loss-of-function SIRT3 polymorphism was associated with the presence of idiopathic PAH in an unbiased cohort of 162 patients and controls. Patients expressing the polymorphism had greater levels of mitochondrial acetylation (n=10) compared to patients without the polymorphism.

CONCLUSIONS

SIRT3 deficiency may explain several aspects of PAH and should be studied in biomarker discovery and therapeutics programs.

Supervisor: Dr Evangelos D. Michelakis

A Decrease in Neomycin Contact Sensitization Rates across Western Canada

Mariam Abbas¹, Peter Hull², Gillian de Gannes³, Reza Toussi¹, Azita Milani¹, John Elliott¹,
Supervisor: Dr. John Elliott

INTRODUCTION

Rates of contact sensitization to neomycin range from 7-13% in North America, while in Europe the rate averages 1.9%. This variation may largely be influenced by the reduced availability of neomycin in topical products in Europe. Neomycin products are no longer readily available in Canada; therefore we examined what influence this may have had on neomycin sensitization rates in the three western provinces.

METHODS

Based on an observation originally communicated by LM Parsons and C Zhang from the University of Calgary, we undertook a multicenter, retrospective study of 5690 patient charts from the 3 other western Canadian Universities where patch test results are available (Saskatchewan (UofS), Alberta (UofA), and British Columbia (UBC)). Data was available from 2001-2013 for UofS (except 2006), whereas UofA and UBC had data from 2009-2013. Descriptive statistics, trend analysis, and risk estimates were determined. Statistical analyses were performed using SPSS, version 20.

RESULTS

The mean patient age for neomycin sensitization was 49.5 years (95% Confidence Interval (CI): 47.3-51.7); with a female predominance of 82.1%. Prevalence rates of neomycin sensitization at UofS dropped significantly from 7.37% (2001-2008) to 1.66% (2009-2013). UofA and UBC had similar prevalence rates at 1.44% and 2.08% respectively (2009-2013). Regression analysis found that the neomycin sensitization rates for 2001-2008 dropped by 1.16% per year (UofS) while the overall drop from 2001-2013 was 0.89% per year. Analysis of Variance (ANOVA) determined that location did not significantly impact neomycin sensitization rates from 2009-2013 (p -value= 0.587). Gender was found to positively influence neomycin sensitization (p <0.001). Relative risk (RR) estimate (RR=2.75; 95% CI, 1.86-4.06) indicates that females are 2.75 times more likely to be sensitized.

CONCLUSIONS

Sensitization rates for neomycin have decreased in Western Canada, and are in fact now similar to Europe. This trend is likely influenced by the reduced availability of over-the-counter and prescription neomycin products in Canada.

Supervisor: Dr. John Elliott

Rare Central Nervous System Complication Secondary To Klebsiella Pneumoniae Infection.

Emad Saad MD, Emad A. Barsoum MD, Boyington Curtiss MD.
Supervisor: Dr Boyington Curtiss MD.

INTRODUCTION

Klebsiella pneumonia is typically implicated in respiratory and urinary tract infections. A hypervirulent strain (hypermucoviscous capsular serotype K1) that causes liver abscesses with potential spread to lung, brain, and other organs has been increasingly reported, particularly in Southeast Asia. Complications can include endophthalmitis and meningitis. We describe a case with an unusual late neurologic complication.

METHODS

A 54 year-old male of Asian descent was brought to the emergency department with confusion, fever and chills. His past history was significant for remote treated active tuberculosis and longstanding alcoholism. Physical examination was unremarkable except for fever (38.3 C), scleral icterus and slurred speech. Laboratory work up showed a high white cell count (16400 cells/ml), elevated liver transaminases (ALT 83 U/L) and high total bilirubin (24 umol/L). Computed Tomography scan (CT) of the chest revealed multiple lungs nodules. CT abdomen-pelvis showed a hepatic abscess measuring 4 cm in diameter. Magnetic resonance imaging (MRI) of the brain showed innumerable rim enhancing cystic lesions within both cerebral hemispheres.

Culture of Klebsiella pneumoniae was achieved from urine, bronchoalveolar lavage and lung biopsy. Cultures for tuberculosis were negative, as was HIV serology.

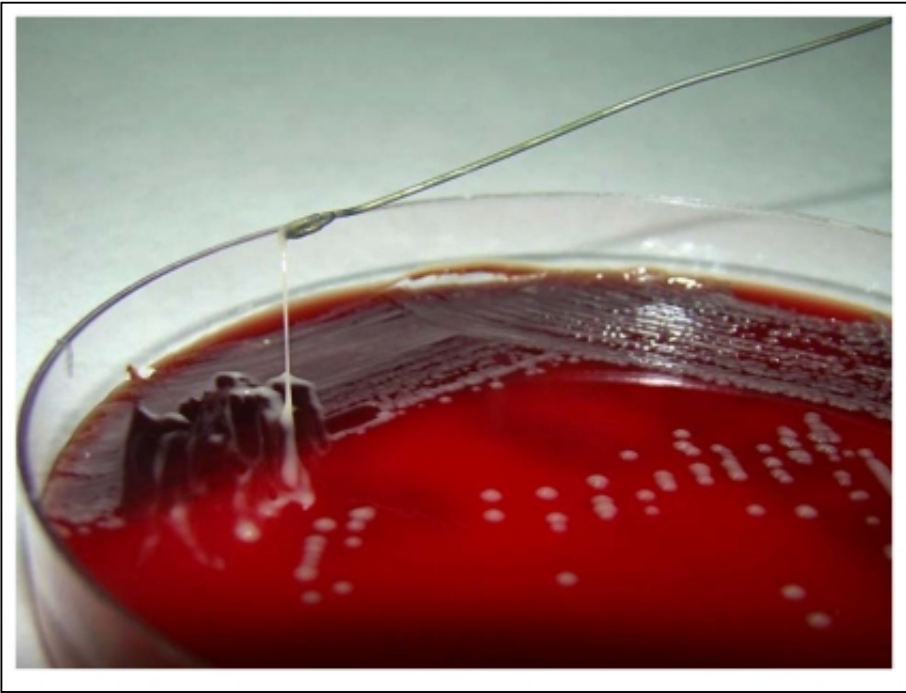
RESULTS

The patient was placed on intravenous ceftriaxone with initial significant improvement. However, approximately two months into his treatment, he developed a dramatic worsening in cognition, with aphasia and worsened motor function. A communicating hydrocephalus was diagnosed on repeat imaging. He required transfer to neurosurgery for placement of a ventriculoperitoneal shunt that resulted in dramatic improvement of his symptoms. Resolution of his liver and lung abscesses and stabilization of his brain abscesses was achieved after over four months of treatment.

CONCLUSIONS

This case demonstrates the metastatic potential of highly virulent strains of Klebsiella pneumoniae. As well, the case highlights the need for ongoing assessment as neurologic complications may develop well after initial presentation.

Supervisor: Dr Boyington Curtiss MD.



Living donor lobar lung transplantation for scleroderma-associated usual interstitial pneumonia: 8 years and counting

Cheryl Laratta¹, Kathy Jackson², Lakshi Puttagunta³, John Mullen^{2,4}, Dale Lien^{2,5}, Justin Weinkauff^{2,5}

Supervisor: Dr. Justin Weinkauff

INTRODUCTION

Scleroderma-associated interstitial lung disease is a life-limiting complication of scleroderma, and often precedes transplantation. Living donor lobar lung transplantation (LDLLT) is a viable alternative in specialized centres to deceased donor lung transplantation under select circumstances.

METHODS

A case review was performed at the University of Alberta Hospital, Edmonton, Alberta.

RESULTS

Clinical Case: A 47 year old female underwent LDLLT after nine years of symptomatic scleroderma-associated usual interstitial pneumonia and three years awaiting deceased donor lung transplantation. Her manifestations of scleroderma include mild sclerodactyly, periungual erythema, Raynaud's phenomenon, and gastroesophageal reflux, with positive antinuclear autoantibodies. Several years post-transplant, manometry revealed feeble lower esophageal sphincteric pressure with ineffective esophageal motility. Bronchiolitis obliterans syndrome developed 64 months post-transplant without evidence of aspiration or reflux on transbronchial biopsy. Currently, she has normal renal function and good allograft function [FEV1 1.52L (73% predicted) and FVC 2.50L (99% predicted)].

CONCLUSIONS

This is the second reported case of LDLLT in scleroderma, and the first reporting long-term pulmonary, renal and esophageal function.

Supervisor: Dr. Justin Weinkauff

Cushing's Syndrome Related Dilated Cardiomyopathy: Favorable Outcome With Treatment.

Rany Al-agma and Aashna Gill
Supervisor: Dr. Rany Al-agma

INTRODUCTION

A 29 year old male with a history of new onset diabetes and dilated cardiomyopathy, presented to the hospital with acute heart failure and stroke. The ejection fraction was 19%. Endocrinology consultation was sought for management of Diabetes. Hemoglobin A1c was 14.5% (4.3-6.1%). The physical exam revealed findings suspicious for Cushing's syndrome. On evaluation he was found to have an elevated 24 hr urinary cortisol of 702 nmol/24 hrs (normal <230nmol/hr), suppressed ACTH of <5 ng/L (normal 10 to 46 ng/l), and a 4 cm adrenal mass on CT abdomen. Surgical resection was planned.

METHODS

The patient was closely followed pre and post operatively. Review of literature was done using key words Dilated Cardiomyopathy and Cushing's.

RESULTS

Surgical resection was done and pathology confirmed adrenal adenoma. Post-op follow up showed complete reversal of dilated cardiomyopathy with ejection fraction of 55% and hemoglobin A1c of 5.4%. On review of literature 8 similar cases were found. In all these cases there was reversal of dilated cardiomyopathy after treatment of Cushing's.

CONCLUSIONS

Based on our case and review of literature for other cases of dilated cardiomyopathy associated with Cushing's syndrome, we conclude that dilated cardiomyopathy has a favorable outcome after treatment of Cushing's syndrome. We suggest that patients with no other known cause of dilated cardiomyopathy should be carefully evaluated for Cushing's syndrome, as the diagnosis and treatment of Cushing's alters the management and results in complete reversal of this condition.

Supervisor: Dr. Rany Al-agma

ALLERGIC CONTACT DERMATITIS CAUSED BY EXPOSURE TO AN INDUSTRIAL MICROBIAL CONTROL AGENT USED IN THE ALBERTA OILSANDS

Dr. Paul Kuzel, MD; Dr. Jeremy Beach, MBBS, MD, FRCP(Edin), FFOM, FRCP(C); Dr. John Elliott, MD, FRCPC

Supervisor: Dr. John Elliott, MD, FRCPC

INTRODUCTION

Methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) are antimicrobial preservative agents effective against numerous bacteria, yeast and fungi. Both are utilized in a wide variety of commercial and industrial applications, from personal care products to water-based cooling systems.

METHODS

We conducted a retrospective review of a patient who developed widespread allergic contact dermatitis (ACD) following exposure to a water-based microbial control agent (Spectrus™ NX1106) containing a mixture of MI/MCI.

RESULTS

Our 51-year old male patient is employed as a dangerous goods transport driver in the Canadian province of Alberta. Over a four day period, he was required to haul three tanker truckloads full of Spectrus™ NX1106 over a distance of 450km. Despite wearing full personal protective equipment (PPE), the patient developed a severe blistering eruption by day 4, requiring hospitalization for a period of 10 days. Patch testing confirmed a 2+ reaction to MI alone, and a 3+ reaction to a MCI/MI mixture.

CONCLUSIONS

MCI and MI are two closely-related preservative agents used for numerous commercial and industrial applications. Both are associated with a significant risk of ACD, notwithstanding the use of PPE. The combination of MCI/MI may have the potential for synergistic effects in patients who develop ACD.

Supervisor: Dr. John Elliott, MD, FRCPC

Frequency of atrial arrhythmias in stroke: Prolonged monitoring of cardiac rhythm for detection of Atrial Fibrillation After a Cerebral Ischemic Event (PEACE) study

I. Yaseen MD1, G. Basir MD1, E. Ghrooda MD1, A. Mohammad PhD1, N. Khan, A. Tahir, P. Dobrowolski MD1, A. Nadeem, M. Hasan MD1, Gulamhusein MD, FRCPC2 and A. Shuaib MD, FRCPC1
Supervisor: Prof. Ashfaq Shuaib

INTRODUCTION

Recent studies suggest that prolonged cardiac monitoring may identify paroxysmal atrial fibrillation (PAF) in up to 18% of patients with cryptogenic stroke. PAF can also be a potential etiology where another potential mechanism is present. We prospectively monitored patients presenting with a TIA or stroke where preliminary investigations (including a Holter) did not show atrial fibrillation.

METHODS

Prospective non-randomized study of patients with TIA and acute stroke between September 2012 and September 2013 where Spider Flash-t™ Monitors (Sorin Group, Italy) were attached to the patients for prolonged monitoring. Clinical events were evaluated with a specifically designed 'arrhythmia score' and the recordings were initially reviewed by the study team and then by the study cardiologist. The duration and frequency of PAF was recorded and the results were conveyed to the referring stroke neurologist.

RESULTS

In 102 patients (duration of monitoring 14 (\pm 4) days), there were 39 patients (38.2%) with PAF (AF >30 seconds 12 patients, AF and <30 sec 27 patients). Atrial flutter was detected in an extra four patients and paroxysmal atrial tachycardia was detected in additional 12 patients. In three PAF, was evident with concomitant symptomatic large vessel carotid disease. The diagnosis of PAF leads to initiation of anticoagulant treatment in 31 patients.

CONCLUSIONS

Prolonged cardiac monitoring for detection of atrial arrhythmias increases the yield for PAF. Previous studies have focused on patients with cryptogenic stroke. Our study shows that PAF and other arrhythmias are present with similar frequency in patients where additional mechanisms may account for the etiology and often results in changes in treatment.

Supervisor: Dr. Prof. Ashfaq Shuaib

Dietary fat intake and high fecal calprotectin predict relapse of ulcerative colitis patients

Ammar Hassanzadeh Keshteli, Florisvan den Brand, Karen Kroeker, David Wishart, Rhonda Bell, Janis Baarda, Rupasri Mandal, Rosica Valcheva, Karen Madsen, Levinus A Dieleman
Supervisor: Dr. Karen Madsen

INTRODUCTION

The aim of the present study was to investigate the relationship between dietary intake and disease relapse in patients with ulcerative colitis (UC) and determine if fecal calprotectin (FC) or specific metabolic profiles in urine or serum would be predictive of disease relapse.

METHODS

A prospective cohort study was conducted on adult UC patients in remission. Assessment of dietary intake was performed using a 24-hour dietary recall and a food frequency questionnaire. Metabolomic profiling was performed on serum and urine samples using nuclear magnetic resonance spectroscopy and mass spectrometry. Stool samples were collected for FC measurement.

RESULTS

Twenty UC patients in remission were included (55%female, age:42.7±14.7 y) and followed for up to 12.12±1.86 months. Seven patients (35%) relapsed during the follow-up period. Overall, 71.4% of patients with high FC (>150 µg/g) and 15.4% of those with normal FC at baseline relapsed (RR: 4.64, 95%CI 1.35-15.91). Mean energy-adjusted fat intake (69.6±8.2vs 60.7±5.6 g/day, P=0.02) and mean energy-adjusted monounsaturated fat intake (28.9±4.1 vs 24.0±2.2 g/day, P=0.03) were significantly higher in patients who relapsed versus those who remained in remission. 181 and 216 metabolites were identified in serum and urine samples respectively. Partial least-squares discriminant analyses of baseline samples clustered those patients who subsequently relapsed (Figure1). There was a positive correlation between carbohydrate intake and serum pyruvate. Fat intake was inversely correlated with urine acetamide and associated with increased serum 2-hydroxy butyrate. Saturated fatty acid intake was inversely correlated with urine acetamide and was associated with increased urine serotonin.

CONCLUSIONS

High fat intake and high fecal calprotectin levels were associated with subsequent relapse in UC patients. Furthermore, novel serum and urine metabolites related to dietary intake were identified to be associated with those patients who subsequently relapsed. Interestingly, metabolites predicting relapse involved both short and long term dietary intake, host metabolism and gut bacterial function.

Supervisor: Dr. Karen Madsen

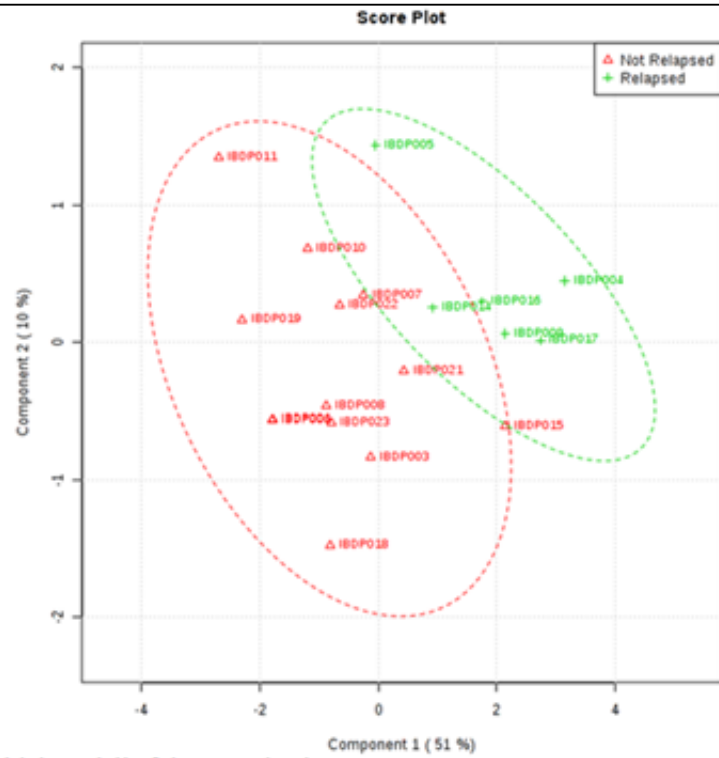
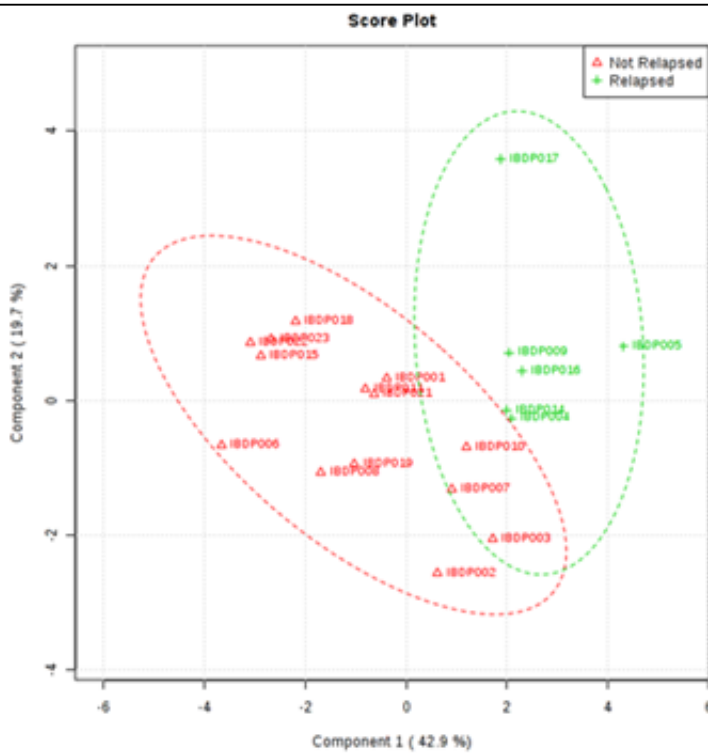


Figure 1. PLSDA plots based on urine (left) and blood (left) metabolomics measurements at baseline could discriminate between ulcerative colitis patients who relapsed and who were still in remission during follow up.