Research DAY
Department of Medicine 2013

GRADUATE STUDENTS | RESIDENTS | POSTDOCTORAL FELLOWS

THURSDAY, MAY 16, 2013

ORAL PRESENTATIONS

CLASSROOM D

2F1.04 WALTER MACKENZIE CENTRE

POSTER PRESENTATIONS

LOWER LEVEL

JOHN W SCOTT HEALTH SCIENCES LIBRARY

Chair's Welcome

Barbara J. Ballermann, MD

"Welcome to our Research Day - one of the most important and rewarding days in our academic year! It is a day 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 we are fortunate to have as our guest oral adjudicator, Dr. Roger Hajjar, Director of the Cardiovascular Research Center at the Mount Sinai School of Medicine in New York.

Research Day gives the opportunity for all Department members and guests to interact with our young researchers. We currently have a total of 71 Graduate Students, 29 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."

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

"...one of the strongest motives that lead men to art and science is escape from everyday life with its painful crudity and hopeless dreariness, from the fetters of one's own ever-shifting desires. A finely tempered nature longs to escape from the personal life into the world of objective perception and thought."

Albert Einstein

As much as you can

And if you can't shape your life the way you want,
at least try as much as you can
not to degrade it
by too much contact with the world,
by too much activity and talk.

Try not to degrade it by dragging it along,
taking it around and exposing it so often
to the daily silliness
of social events and parties,
until it comes to seem a boring hanger-on.

Constantine Cavafy
(a Greek poet, ~1926)

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Research Day Guest Adjudicator

Roger Hajjar, MD

Dr. Hajjar is currently the Director of the Cardiovascular Laboratory of Integrative Physiology and Imaging at the Massachusetts General Hospital in Boston, MA, the Director of the Cardiovascular Research Center at the Mount Sinai School of Medicine in New York & the Director of the Cardiology Fellowship Program at the Mount Sinai School of Medicine.

He earned his medical degree from the Harvard Medical School and Harvard-M.I.T., Division of Health, Sciences and Technology in Boston in 1990. His residency training in Internal Medicine and fellowship in Cardiology was done at the Massachusetts General Hospital and Harvard Medical School before completing his Clinical and Research Fellowship in 1997.

"Our laboratory's main focus is in cardiac gene therapy for heart failure and we have validated the cardiac sarcoplasmic reticulum calcium ATPase pump, SERCA2a, as a target in heart failure, developed methodologies for cardiac directed gene transfer that are currently used by investigators throughout the world, and examined the functional consequences of SERCA2a gene transfer in failing hearts. Our laboratory has specific interests in calcium cycling in failing hearts and targeted gene transfer in various animal models. The significance of our work research has been recognized with the initiation and recent completion of phase 1 and phase 2 First-in-Man clinical trials of SERCA2a gene transfer in patients with advanced heart failure."

Research Day Guest Adjudicator

Richard Lehner, PhD

Dr. Lehner obtained his PhD in Biochemistry at the University of Toronto, followed by post-doctoral training at the CNRS in Marseille, France and at the University of Alberta. He joined the Department of Pediatrics at the University of Alberta as an Assistant Professor in 1998 with cross-appointment in the Dept. of Cell Biology. In 2008 Dr. Lehner was appointed Director of the Group on Molecular and Cell Biology of Lipids.

Current Research Interests:

Triacylglycerol (TG, also commonly referred to as fat) is the most concentrated form of energy storage in humans. Excessive TG storage is manifested as obesity, which is a major health problem in the Western world. Obesity is a risk factor for hypertension, diabetes and cardiovascular disease. Therefore, there is a substantial pharmaceutical interest in the enzymes that control TG metabolism in tissues. Our research is focused at elucidating the mechanism by which TG is utilized in the liver, intestine, adipose and other tissues.

Panel of Judges

Roger Hajjar, MD
Director of the Cardiovascular Research Center
Mount Sinai School of Medicine
New York

Richard Lehner, PhD
Professor of Pediatrics
Director, Group on Molecular and Cell Biology of Lipids
University of Alberta

Barbara J. Ballermann, MD
Professor of Medicine
Chair, Department of Medicine
University of Alberta

Session Chairs

Dr. Gavin Oudit
Chair, Research Day Committee

Dr. Darryl Rolfson
Director, Postgraduate Medical Education

Meeting at a Glance

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11:00-1:00	Poster Presentations and **Lunch**
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Poster Presentations

Core Internal Medicine & Subspecialty Residents, Graduate Students & Post Doctoral Fellows

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Poster Presentations

Core Internal Medicine & Subspecialty Residents, Graduate Students & Post Doctoral Fellows

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Poster Presentations

Core Internal Medicine & Subspecialty Residents, Graduate Students & Post Doctoral Fellows

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Core Internal Medicine & Subspecialty Residents, Graduate Students & Post Doctoral Fellows

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

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

Severe muscle mass loss in cirrhosis-Can bedside tools be used to predict a CT or MRI diagnosis of sarcopenia?

L. Zenith1, R.P. Myers2, H. Qamar1, N. Mansoor1, M. Carbonneau1, L. Gramlich1, G. Low3, M. Ma1, P. Tandon1
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

Sarcopenia assessed at the 3rd lumbar vertebral level is an independent predictor of mortality in cirrhosis patients. Although predictive of mortality, the need for cross-sectional imaging limits the practical use and repeatability of the assessment. The objective of this study was to evaluate the correlation of bedside assessment tools with a cross-sectional imaging diagnosis of sarcopenia.

METHODS

Prospective data-collection in outpatients with cirrhosis. Exclusion criteria:HCC or other malignancy, significant cardiopulmonary disease. Average feather index(ultrasound probe held lightly over muscle) is the height corrected average of quadriceps muscle thickness at 2 pre-defined sites. Average compression index, mid-arm-muscle-circumference, mid-arm-circumference, hand-grip, and subjective global assessment were also evaluated. Pearson’s correlation coefficients and AUROC were used to evaluate the relationship between the bedside nutritional assessment methods and sarcopenia.

RESULTS

159 patients were evaluated, 43% had sarcopenia (57% of males and 25% of females). For most tested variables, there was a moderate to strong correlation coefficient and high AUROC values for the prediction of sarcopenia, but within each measure there was considerable overlap between patients with and without sarcopenia. Therefore, using logistic regression, a sarcopenia predictive model was developed. The model with the best AUROC and the fewest variables included BMI and Avg feather index. The respective odds ratios (95% CI) were 0.88(0.79-0.98) and 0.081(0.012-0.54) with an AUROC of 0.78 for males, and 0.74(0.62-0.89) and 0.036(0.002-0.76) with an AUROC of 0.89 for females. Cut points of ≥0.61 and ≥0.25 yielded a sensitivity of 72% and 94% and specificity of 78% and 76% for males and females respectively.

CONCLUSIONS

A single bedside measure is unable to provide an accurate diagnosis of cross-sectional imaging based sarcopenia. A combination of variables (BMI, thigh ultrasound) provides a useful model. It remains to be seen whether any of the bedside measures will be as predictive of clinical outcome as cross-sectional imaging has been.

Supervisor: Dr. Puneeta Tandon

Uncoupling protein 2 deficiency mimics hypoxia and endoplasmic reticulum stress in mitochondria and triggers pseudo-hypoxic pulmonary vascular remodeling

Dromparis P, Paulin R, Sutendra G, Qi AC, Bonnet S, and Michelakis ED.
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Mitochondrial signaling regulates both the acute and chronic response to hypoxia in the pulmonary vasculature, and suppressed mitochondrial glucose oxidation (GO) contributes to the apoptosis-resistance and proliferative diathesis in the vascular remodeling in pulmonary hypertension (PHT). Hypoxia directly inhibits GO, while endoplasmic reticulum (ER)-stress can indirectly inhibit GO by decreasing mitochondrial calcium levels. Both hypoxia and ER-stress can cause PHT. Uncoupling protein 2 (UCP2) has been shown to conduct calcium from the ER to mitochondria. We hypothesized that UCP2 deficiency reduces mitochondrial calcium (Ca2+m) in pulmonary artery smooth muscle cells (PASMCs), inhibiting GO and mimicking the effects of hypoxia and ER-stress on mitochondria.

METHODS

Isolated 4th generation PASMCs were exposed to normoxia (pO2~120mmHg) or hypoxia (pO2~40mmHg). Ca2+m (4mtD3CPV chameleon plasmid) was assessed under baseline and histamine- (100μm) stimulated conditions. Cytosolic calcium (FLUO3), ER-mitochondrial proximity (electron microscopy) mitochondrial hyperpolarization (TMRM), mitochondrial-derived reactive oxygen species (mROS) (MitoSOX), pyruvate dehydrogenase activity, Krebs' metabolites (mass spectroscopy), hypoxia inducible factor 1α (HIF1α; luciferase, immunofluorescence, immunoblot), 0.1%FBS-induced apoptosis (TUNEL) were assessed. In vivo, PHT determined by mean pulmonary artery pressure (mPAP; Millar catheter), echocardiography, total pulmonary resistance (TPR = mPAP/CO), medial wall thickness (H&E stain), muscularization and proliferation (immunohistochemistry).

RESULTS

Ucp2KO-PASMCs had lower Ca2+m than Ucp2WT-PASMCs at baseline and during histamine-stimulated ER-Ca2+ release, despite normal ER-mitochondria contact. Normoxic Ucp2KO-PASMCs had mitochondrial hyperpolarization, lower Ca2+-sensitive mitochondrial enzyme (PDH) activity, reduced mROS and Krebs' cycle metabolites and increased resistance to apoptosis, mimicking the hypoxia-induced changes in Ucp2WT-PASMC. Ucp2KO mice spontaneously developed pulmonary vascular remodeling and PHT and exhibited a pseudohypoxic state with pulmonary vascular and systemic HIF1α activation (increased hematocrit), not exacerbated by chronic hypoxia.

CONCLUSIONS

This first description of UCP2 in oxygen sensing and in vascular remodeling may open a new window in PHT biomarker and therapeutic strategies.

LOW ANKLE BRACHIAL INDEX PREDICTS HIGHER CORONARY SYNTAX SCORES AND MYOCARDIUM AT RISK, BUT NOT INCOMPLETE CORONARY REVASCULARIZATION

Meghan Sebastianski, Seshasayee Narasimhan, Olga Toleva, Jay Shavadia, Seraj Abualnaja, Ross Tsuyuki, Michelle Graham and M. Sean McMurtry
Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Peripheral arterial disease is associated with coronary artery disease (CAD) and poor outcomes after coronary revascularization. We hypothesized that patients with low ankle brachial index (ABI ≤ 0.90) have more complex CAD and more myocardium at risk than patients with normal ABI (1.00 ≤ AB I ≤ 1.40) and that their coronary revascularization is less complete.

METHODS

728 consecutive patients were drawn from a prospective cohort of adults referred for coronary angiography. ABI was measured bilaterally using Doppler ultrasound prior to angiography. Blinded reviewers measured Syntax score, Duke Jeopardy score at baseline and at three months. Data was analyzed using one-way ANOVA and multinomial logistic regression. Thresholds for high Syntax score and high Duke Jeopardy score (pre and post revascularization) were calculated using the entire sample means plus one standard deviation, rounded to the nearest integer.

RESULTS

Of 728 patients, 56 had ABI ≤ 0.90, 57 had 0.90 < ABI < 1.00, 563 had 1.00 ≤ ABI ≤ 1.40, and 49 had ABI > 1.40. After adjustment for age, sex, hypertension, dyslipidemia, diabetes and smoking status, patients with ABI ≤ 0.90 had an odds ratio for high syntax score of 3.2 (95% CI 1.2-8.8; p=0.03) compared with the normal ABI group. Similarly, after adjustment the odds ratio for high baseline Duke Jeopardy score was 3.3 (95% CI 1.3-8.1; p=0.009) in the ABI ≤ 0.90 group. The odds ratio for high post-revascularization Duke Jeopardy score was 2.6 (95% CI 0.8-8.4; p=0.104) in the ABI ≤ 0.90 group.

CONCLUSIONS

ABI ≤ 0.90 is associated with higher Syntax scores and more myocardium at risk in patients referred for coronary angiography. We did not find that subjects with ABI ≤ 0.90 have less complete coronary revascularization.

Supervisor: Dr. Ross Tsuyuki

CLIC5A Deficiency Accentuates Kidney Damage in DOCA/Salt Hypertensive Mice

Mahtab Tavasoli1, Laiji Li1, Linfu Zhu2, Thomas Churchill2 and Barbara J. Ballermann1
Supervisor: Dr. Barbara J. Ballermann

INTRODUCTION

Podocytes are highly specialized epithelial cells that extend inter-digitating actin-based foot processes around the exterior of renal glomerular capillaries to buttress the vessel wall against high intra-capillary pressure. Glomerular capillary hypertension is an established risk factor for the development of diabetic nephropathy. CLIC5A was identified in our laboratory as a major protein in glomerular podocytes, where it is a component of the NHERF2-ezrin complex that couples apical podocalyxin to the cellular actin cytoskeleton. We have shown that deletion of CLIC5A in mice leads to ezrin dephosphorylation and disorganization of podocyte foot processes. Here, we hypothesized that lack of CLIC5A might be detrimental under conditions of increased mechanical strain.

METHODS

Hypertension was induced in wild-type (WT) and CLIC5A deficient (CLIC5A-/-) mice using subcutaneous slow-release deoxycorticosterone (DOCA) pellets and 1% saline drinking water (DOCA/Salt), starting 14 days after uninephrectomy. Control mice were subjected to uninephrectomy only. Blood pressure, urinary albumin (Albumin:Creatinine ratio; ACR) and kidney histology, evaluated 20 days after initiation of DOCA/Salt treatment, are reported.

RESULTS

Compared to uninephrectomy alone, DOCA/Salt consistently increased systolic blood pressure in both WT (119±6 vs. 98.9±8 mmHg, $p<0.001$) and CLIC5A-/- mice (121±11.5 vs. 97±8 mmHg, $p<0.001$). As expected, DOCA/Salt treated mice also developed a marked hypokalemic metabolic alkalosis. In WT and CLIC5A-/- mice urine albumin excretion was unaffected by uninephrectomy alone, and DOCA/Salt induced albuminuria in both WT and CLICA-/- mice. However, the urine albumin excretion rate was significantly higher in CLIC5A-/- compared to WT mice (ACR mg/g: 1,720±960 vs. 780±235, $p < 0.05$). Histological analysis by PAS and Trichrome staining revealed more severe fibrosis in the kidney samples from CLIC5A-/- mice, compared to WT.

CONCLUSIONS

The findings are consistent with the hypothesis that CLIC5A serves an important function in stabilizing the extracapillary podocyte buttress that protects against the deleterious effects of glomerular capillary hypertension in mice.

Supervisor: Dr. Barbara J. Ballermann

In vitro and in vivo evidence of epigenetic effects (histone acetylation) of mitochondria-targeting drugs

Zervopoulos SD, Sutendra G, Dromparis P and Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Histone acetylation (the addition of an acetyl group from acetyl-CoA to histone lysine residues) is critical for epigenetic control. Acetyl-CoA is produced in the mitochondria but it cannot cross membranes, reaching the nucleus indirectly via the membrane permeable citrate (a product of the Krebs cycle) and the action of ATP-citrate lyase (ACL), which was recently found in the nucleus. This suggests that targeting mitochondria, an emerging area of therapeutics, may affect large groups of genes via epigenetic mechanisms (also see Kinaird et al from our group). We hypothesized that the mitochondria-targeting small molecule Dichloroacetate (DCA), in addition to its described effects on enhancing Krebs activity and inhibiting mitochondria-dependent apoptosis, will increase nuclear histone acetylation, explaining our previous data, showing regulation of large groups of genes (gene chip), which remained unexplained.

METHODS

We studied the effects of DCA in vitro (A549 non-small cell lung cancer as well as normal cell lines) and in vivo in rats (oral DCA in athymic rat xenotransplant A549 tumors) and in patients (comparing tumors before and after DCA treatment in patients with advanced glioblastoma in a recent clinical trial). We measured acetyl-CoA and Krebs intermediates (Elisa and 1H-NMR) as well as histone acetylation (immunoblots and confocal immunofluorescence of specific acetylated histone residues).

RESULTS

DCA increased acetyl-CoA, citrate and succinate, while decreased lactate levels in A549 but not normal cells, as expected. Levels of acetylated core histone H3 were increased in vitro and in vivo in rat tumors (associated with a significant reduction in tumor size) and in 3 glioblastoma patients who showed clinical response to DCA.

CONCLUSIONS

DCA increases histone acetylation, underlying a connection between mitochondrial metabolism and acetylation-mediated epigenetic regulation. Our data suggest that mitochondria-targeting drugs can have effects beyond mechanisms directly relevant to mitochondrial function (like apoptosis).

Supervisor: Dr. Evangelos Michelakis

Mitochondrial suppression due to loss of Sirt3 deacetylase activity causes pulmonary arterial hypertension (PAH).

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

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by suppressed apoptosis and enhanced proliferation in the pulmonary artery (PA) wall, leading to an obstructive vascular remodeling and premature death. The suppressed apoptosis in the PA wall is partly due to suppressed mitochondrial function, in a manner similar to cancer. 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. Sirt3 KO 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, exposed or not to chronic-hypoxia CH 10% for 3 weeks, as well as monocrotaline MCT-induced PAH in rats. In vitro, we used PASMC isolated from WT and KO SIRT3 mice, with or without exposure to hypoxia.

RESULTS

Normoxic-KO-PASMCs had a global decrease in Kreb’s cycle intermediates (mass spectrometry), increased mitochondrial membrane potential and decreased mitochondrial reactive oxygen species compared to WT-PASMCs, mimicking the profile of WT-PASMC exposed to hypoxia. Normoxic-KO-PASMC also had activation of Hif-1a (luciferase activity assays), confirming a “pseudohypoxic” state, increased proliferation (%Ki67) and suppressed apoptosis (%TUNEL). Compared to WT normoxic mice, KO normoxic mice developed spontaneous PAH (mPAP, 30.9±3.13mmHg vs 14±1.41mmHg), increased RV hypertrophy (RVH, fulton index=0.33±0.026 vs 0.25±0.022) and increased percentage of partially (38% vs 18%) and fully (21% vs 12%) muscularized PAs. In the MCT rat model, intra-tracheal nebulization of Sirt3 adenovirus at day 21-post MCT injection, improved mPAP and vascular remodeling compared to the GFP-only adenovirus treated rats.

CONCLUSIONS

We demonstrated for the first time a critical role of SIRT3 in PAH. The loss of SIRT3 causes a mitochondrial suppression that mimics the suppression caused by hypoxia and may explain the anti-apoptotic and pro-proliferative diathesis in PAH.

Supervisor: Dr. Evangelos D. Michelakis

Vascular Parkinsonism in a Tertiary Care Stroke Prevention Clinic: Prevalence and Development of a New Screening Questionnaire

Herbert A. Manosalva1, Thomas Jeerakathil1, Fabricio Pio1, Maher Saqqur1, Richard Camicioli1 and Oksana Suchowersky1,2
Supervisor: Dr. Oksana Suchowersky, Dr. Thomas Jeerakathil

INTRODUCTION

Vascular Parkinsonism (VasPD) is characterized by Parkinsonism with prominent gait problems associated with cerebrovascular disease occuring within 1 year of the stroke. Few prevalence studies are known, and no standardized diagnostic criteria are available.

METHODS

Consecutive stroke patients were screened in the Stroke Prevention Clinic (SPC) for VasPD, during a period of 4 months, using a validated scale (TQ) for detection of Parkinsonism[1] with a cutoff of ≥4. We developed a 4 point scale (FMAS), based on diagnostic criteria for VasPD suggested by Zijlman[2] (Table 1 and 2). Statistical analysis included calculation of medians and interquartile range and performance of Wilcoxan Rank Sum Tests.

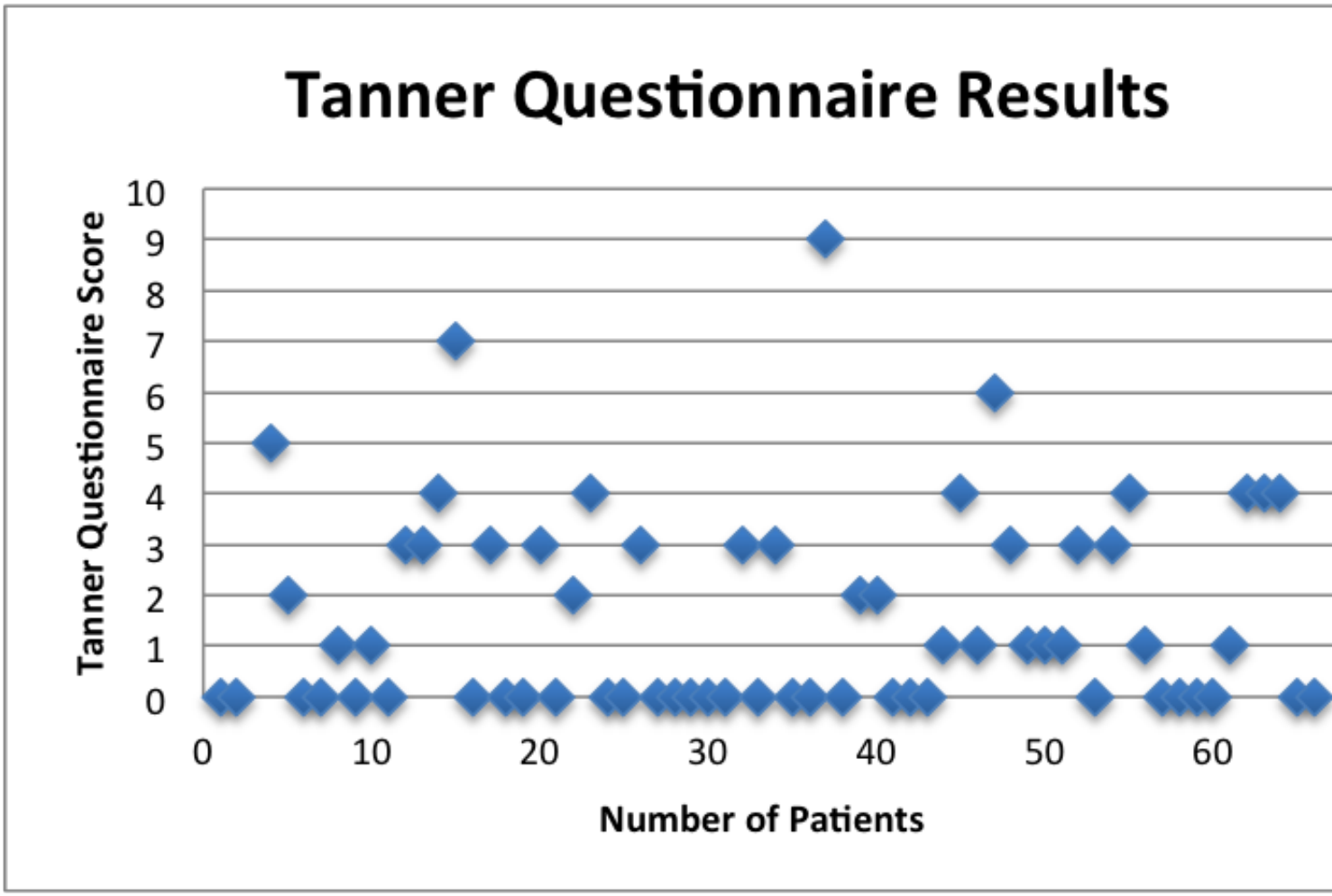
RESULTS

We screened 80 patients, 46% males and 54% females, with a mean age of 65 (range 25 - 95; SD 14.5) in the SPC. Only thirteen patients scored ≥ 4 on the TQ (median 4, IQR 2 vs. median 0, IQR2; $p<0.0001$) (Figure 1). Of the 13 patients, 7 had clinical Parkinsonism, only 3 fullfilled the clinical criteria for VasPD by attaining a score of 4 in the FMAS, and had higher scores on the TQ than the other patients (median 5, IQR 2 vs median 1, IQR 3; $p=0.0076$) (Table 3).

CONCLUSIONS

Prevalence of Parkinsonism in the SPC was 7/80 (8.7%), with prevalence of VasPD being 3/80 (3.7%). In our data the cutoff score of ≥4 in the TQ gave a sensitivity of 100% for detection of patients with parkinsonism, specificity of 92%. The NPV of the TQ was 100%, but the PPV of the TQ was only 54%. Preliminary data using the new FMAS suggest a total score of 4 points is able to diagnose VasPD, and accurately differentiates from other types of parkinsonism, including IPD patients with stroke. The two-step TQ-FMAS appears to be an useful tool for the screening of patients with VasPD. Further data collection is ongoing.

Supervisor: Dr. Oksana Suchowersky, Dr. Thomas Jeerakathil


Tanner Questionnaire Results
Tanner Questionnaire Score
10
9
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
Number of Patients

Loss of p47phox subunit of NADPH oxidase enhances susceptibility to heart failure due to dysregulation of the myocardial intracellular cytoskeleton: Insight from explanted failing human hearts

Vaibhav B. Patel1,2, Pavel Zhabyeyev1,2, Dong Fan2,3, Wang Wang2,3, Subhash K. Das1,2, Ratnadeep Basu2,3, Zuocheng Wang1,2, Zamaneh Kassiri2,3, Gavin Y. Oudit1,2,3
Supervisor: Dr. Gavin Y. Oudit

INTRODUCTION

The classical phagocyte NADPH oxidase (gp91phox or Nox2) is expressed in the heart. Nox2 activation requires membrane translocation of the p47phox subunit and is linked to heart failure. We hypothesized that loss of p47phox subunit will result in decreased ROS production and resistance to heart failure.

METHODS

Eight weeks old male p47phox null (p47phoxKO) mice, Nox2 null (Nox2KO) mice and wildtype (WT) mice were subjected to transverse aortic constriction (TAC)-induced pressure-overload.

RESULTS

Contrary to our hypothesis, p47phoxKO mice showed markedly worsened systolic dysfunction in response to pressure-overload at 5 weeks and 9 weeks post-TAC compared to WT-TAC mice, whereas Nox2KO mice showed preserved systolic function in response to pressure-overload at 5 weeks. We found that biomechanical stress upregulated N-cadherin, β-catenin, p-Src and Src in p47phoxKO hearts but disrupted the actin filament cytoskeleton and reduced phosphorylation of FAK. In contrast, Nox2KO hearts showed intact actin filament cytoskeleton. p47phox interacts with cytosolic cortactin by co-immunoprecipitation and double immunofluorescence staining in murine and human hearts and translocated to the membrane upon biomechanical stress where cortactin interacted with N-cadherin resulting in adaptive cytoskeletal remodeling. Explanted human hearts also showed increased cortactin and N-cadherin interaction. However, p47phoxKO hearts showed impaired interaction of cortactin with N-cadherin resulting in loss of biomechanical stress-induced actin polymerization and cytoskeletal remodeling. Interestingly, Nox2KO hearts showed preserved interaction between cortactin and N-cadherin resulting in adaptive cytoskeletal remodeling.

CONCLUSIONS

We showed a novel role of p47phox subunit beyond and independent of NADPH oxidase activity, as a regulator of cortactin and adaptive cytoskeletal remodeling leading to a paradoxical enhanced susceptibility to biomechanical stress and heart failure.

Supervisor: Dr. Gavin Y. Oudit

Microarray diagnosis of T cell-mediated rejection in kidney transplant biopsies: the INTERCOM study

Andre Pereira, MD1, Jeff Reeve, PhD1, Jessica Chang, BSc.1, Arthur Matas, MD2, Michael Picton, MD3, Declan De Freitas, MD3, Jonathan Bromberg, MD4, Daniel Seron, MD5, Joana Sellares, MD5, Gunilla Einecke, MD6, Philip F. Halloran, MD1
Supervisor: Dr Philip Halloran

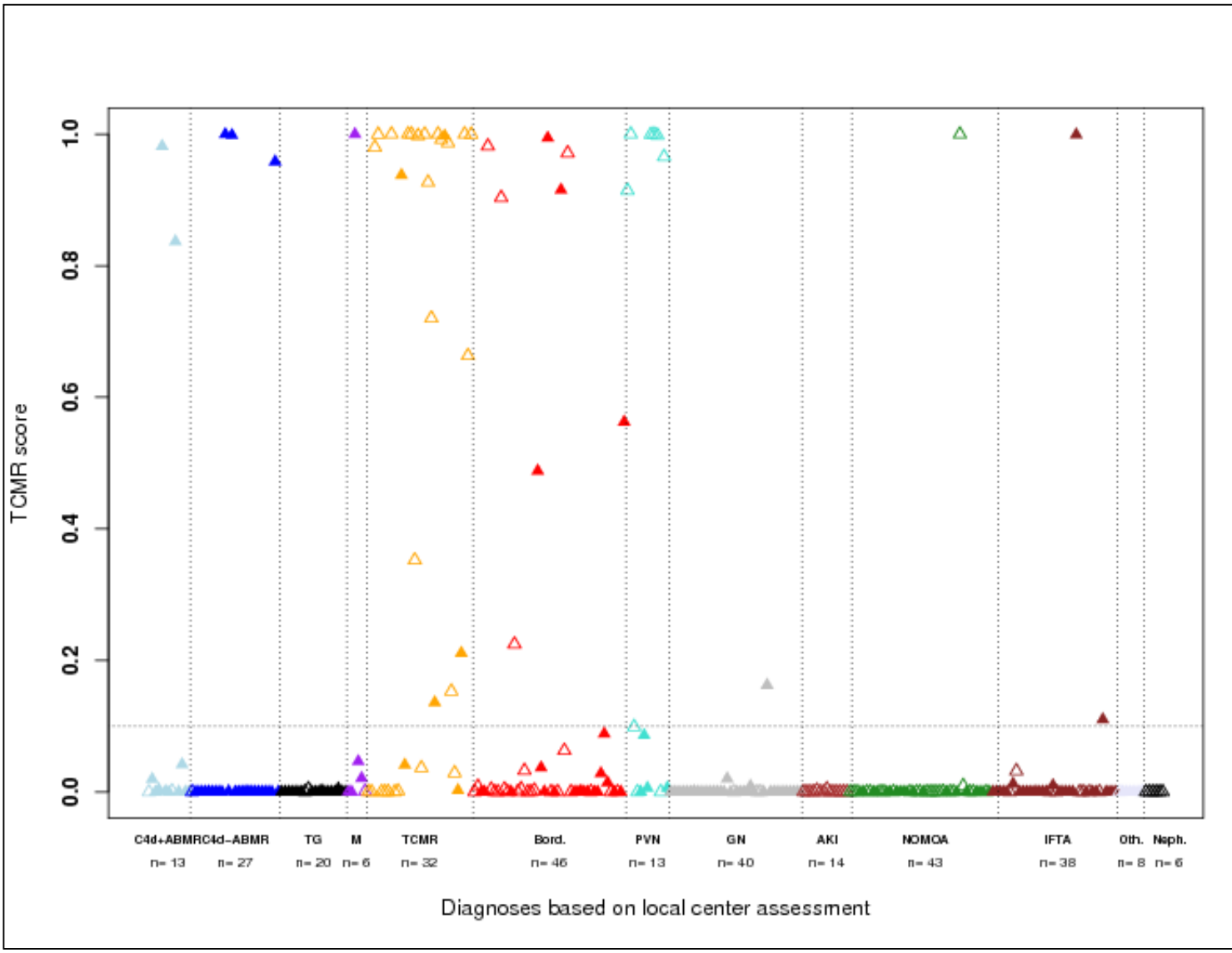
INTRODUCTION
T cell-mediated rejection (TCMR) in kidney transplants is a prototypic inflammatory disease diagnosed by histology. We previously developed a microarray-based test for TCMR in a reference set of 403 biopsies. To examine the potential impact of this test on current practice, we undertook INTERCOM, a prospective international study of 300 new indication biopsies from 264 patients.

METHODS
Biopsies from six centers - Baltimore, Barcelona, Edmonton, Hannover, Manchester, and Minneapolis – were analyzed by microarrays, assigning TCMR scores by an algorithm developed in the reference set. The scores were compared to local histology assessment.

RESULTS
The biopsy TCMR score correlated with histologic TCMR lesions - tubulitis and interstitial infiltration - but not with lesions of other diseases such as antibody-mediated rejection. The accuracy of the TCMR score for primary histologic diagnoses (0.87) was similar to the reference set (0.89). The TCMR scores reclassified 76 of 300 biopsies (25%): 16 histologic TCMR were molecularly non-TCMR; 23 histologic non-TCMR were molecularly TCMR (including six with polyoma virus nephropathy and eight labeled “borderline”); and 38 “borderline” biopsies were molecularly non-TCMR. As in the reference set, most discrepancies were attributable to histology under-diagnosis (e.g. in polyoma virus nephropathy and in scarring) or over-diagnosis e.g. inflammation induced by injury. Neither the TCMR score nor histologic TCMR was associated with graft loss.

CONCLUSIONS
TCMR in kidney transplant biopsies can be diagnosed by microarray analysis, without knowledge of histology, and may help correct errors and reduce ambiguity (borderline cases). These results suggest that up to 25% of biopsies are misclassified when TCMR is assessed by histology, and that many of these errors can be corrected by a microarray analysis. (ClinicalTrials.gov NCT01299168).

Supervisor: Dr Philip Halloran


TCMR score
0.0
0.2
0.4
0.6
0.8
1.0
C4d+ABMR n= 13
C4d−ABMR n= 27
TG n= 20
M n= 6
TCMR n= 32
Bord. n= 46
PVN n= 13
GN n= 40
AKI n= 14
NOMOA n= 43
IFTA n= 38
Oth. n= 8
Neph. n= 6
Diagnoses based on local center assessment

Outcome of weekday vs weekend presentation in NSTEMI

Deirdre O'Neill, Danielle A Southern, Blair O'Neill, Michelle Graham
Supervisor: Dr. Michelle Graham

INTRODUCTION

There is a debate over whether patient care and mortality rates worsen based on weekday versus weekend admission. In non-ST elevation MI (NSTEM), early-invasive management is known to be beneficial. However, since treatment strategies for NSTEMI are urgent rather than emergent, decisions to postpone interventions based upon weekend hospital admission could affect patient outcome. This is particularly relevant in a healthcare system where access to treatment is centralized, requiring triage and transfer over geographically disparate areas. Currently, results of investigations of NSTEMI patients who present on weekends are conflicting.

METHODS

Using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease, a clinical outcomes initiative capturing all cardiac patients in Southern Alberta, we compared time to cardiac catheterization and crude and risk-adjusted mortality for NSTEMI patients presenting on weekdays versus weekends.

RESULTS

From April 1, 2005 to October 31, 2010, 11, 981 patients with NSTEMI were admitted to care facilities in Southern Alberta (32.1% admitted on weekends and 67.9% admitted on weekdays). Baseline characteristics were similar with the exception of more hypertension in the weekday group. Mean time to cardiac catheterization was 2.8 days in the weekend group, compared to 2.6 days in the weekday group ($p=0.03$), with 34.7% of weekend and 45.1% of weekend patients receiving treatment within 24 hours of admission ($p<0.0001$). The crude hazard ratio (HR) for 1-year mortality in the weekend group was 1.10 (95% CI 0.94,1.29). After adjusting for baseline risk factor differences, the HR remained non-significant (HR1.09, CI 0.93,0.27).

CONCLUSIONS

In a large unselected population of NSTEMI patients admitted to institutions across Southern Alberta, weekend presentation was associated with increased delays (4.8 hours) in time to catheterization, but not with increased mortality.

Supervisor: Dr. Michelle Graham

Management and outcomes of venous thromboembolic events in patients with concomitant cancer-associated thrombocytopenia: a retrospective cohort study

Ilana Kopolovic
Supervisor: Dr. Cynthia Wu

INTRODUCTION

Hospitalized cancer patients have increased incidences of venous thromboembolism(VTE) and thrombocytopenia. Thrombocytopenia increases the risk of hemorrhage but does not confer protection against VTE. Optimal management of VTE in patients with thrombocytopenia is not established, and outcomes are largely unknown. We sought to (1)describe a cohort of hospitalized cancer patients with acute VTE and concomitant thrombocytopenia, (2)describe management strategies implemented in this cohort (3)determine incidences of and factors associated with subsequent thrombotic and hemorrhagic outcomes.

METHODS

Retrospective cohort study of all patients admitted to the University of Alberta Hospital's hematology service, or the Cross Cancer Institute, between 2006-2011. Adult patients (>17 yrs) with VTE and thrombocytopenia (plt<100) were included. Outcomes of interest were hemorrhagic and thrombotic events within 3 months of index VTE.

RESULTS

Seventy-four patient charts were reviewed. Patient characteristics are shown in Table 1. Seventeen(23.0%) patients did not receive anti-thrombotic therapy, 30(40.5%) completed at least 3 months of therapeutic anticoagulation, and 27(36.5%) received a modified course of anticoagulation. Over the 3-month period following the index VTE, 29(39.2%) patients experienced 36 events; 23(31.1%) experienced a second symptomatic thrombotic event, and 13(17.6%) suffered clinically significant bleeding (WHO class ≥2). Factors associated with recurrent thrombosis included not having received a full course of anticoagulation (87.0% vs. 47.1%,p= 0.002), hematologic malignancy (95.7% vs. 66.7%,p=0.01), prolonged thrombocytopenia (p=87.0% vs. 58.8%,p=0.03), upper-extremity DVT as the index event (65.2% vs. 31.4%,p= 0.01) and any non-pulmonary embolism index event (87.0% vs. 52.9%,p=0.008). The only factor significantly associated with hemorrhage was hematologic malignancy (100% vs. 70.5%,p=0.036). There were a total of 23 deaths; none were attributed to hemorrhage, and two were due to pulmonary embolism.

CONCLUSIONS

Management of VTE in thrombocytopenic patients remains an area of clinical equipoise, with heterogeneous management strategies employed at our institution and optimal management ill-defined. This population carries a high risk of both early hemorrhage and recurrent thrombosis.

Table 1. Patient characteristics	
Age (mean, (SD))	59 (15)
Male (no., %)	35 (47.3)
Malignancy (no., %)	
hematologic malignancy	56 (75.7)
solid tumor	18 (24.3)
Undergoing chemotherapy (no., %)	
yes	48 (64.9)
no	26 (35.1)
Platelet count (median [IQR])	
at VTE diagnosis	49 [28,78]
nadir	15 [8,46]
Etiology of thrombocytopenia (no., %)	
cytotoxic chemotherapy	26 (35.1)
marrow involvement with cancer	15 (20.3)
chemotherapy & marrow involvement	19 (25.7)
immune-mediated	4 (5.4)
unknown /other	10 (13.5)
Duration thrombocytopenia (no., %)	
<1 month	24 (32.4)
≥1 month	50 (67.6)
Site of index VTE (no., %)	
proximal limb DVT	52 (70.3)
lower extremity	21 (28.4)
upper extremity	31 (41.9)
catheter-associated	28 (37.8)
pulmonary embolism	27 (36.5)
other site	3 (4.1)

Differential elevation in plasma angiotensin-converting enzyme 2 activity in patients with heart failure: effects of gender

Brendan Putko, Zuocheng Wang, Jennifer Lo, Seyyed M. Kazemi-Bajestani, Jason R. Dyck and Gavin Y. Oudit
Supervisor: Dr. Gavin Y. Oudit

INTRODUCTION
Angiotensin-converting enzyme 2 (ACE2) is a negative regulator of the renin-angiotensin system. Plasma ACE2 activity in patients with heart failure (HF) might be a biomarker reflective of disease progression. To assess this, we analyzed plasma from healthy controls and patients with different types of HF.

METHODS
As part of the Alberta HEART (Heart Failure Etiology and Analysis Research Team) project, plasma ACE2 activity was measured indirectly using a fluorescence assay in samples collected from patients with a clinical diagnosis of HF and reduced ejection fraction (EF) (HFrEF, LVEF<35%; n=118, 77% male), or preserved EF (HFpEF, LVEF>50%; n=92, 51% male), and age and gender-matched healthy controls with no history of cardiovascular disease or diabetes (n=49, 42% male).

RESULTS
Compared to control (mean±SEM; 25±2 pmol/hr/mL), plasma ACE2 activity was significantly higher in HFrEF (52.8±3.2 pmol/hr/mL; $p<0.001$), and non-significantly higher in HFpEF (36.1±3.1 pmol/hr/mL; $p=0.059$). A significant difference was seen between males and females in control (31.5±4.4 vs. 20.5±1.9 pmol/hr/mL, respectively; $p=0.014$) and HF cohorts (50.8±2.9 vs. 35.8±3.4 pmol/hr/mL, respectively; $p=0.002$), while there was no significant difference in plasma ACE2 activity in response to obesity, hypertension or diabetes. Plasma ACE2 activity reflected the difference between BNP levels for HFpEF (129.9±20.9 pg/mL) and HFrEF (287.4±32.2 pg/mL), and associated with worsening NYHA functional class (I&II, 42.9±2.6 pmol/hr/mL vs. III&IV, 50.5±4.3 pmol/hr/mL; $p=0.112$). Patients prescribed mineralocorticoid receptor antagonists had significantly higher plasma ACE2 activity (50±3 vs. 37±3 pmol/hr/mL; $p=0.003$), while no other drugs showed significant differences.

CONCLUSIONS
Plasma ACE2 activity is increased in both types of HF; is significantly increased in males and patients prescribed mineralocorticoid receptor antagonists; and is similar within risk factor subgroups. This suggests a potential utility of ACE2 as a prognostic biomarker in HF, particularly in patient subpopulations where traditional biomarkers may have reduced efficacy.

Supervisor: Dr. Gavin Y. Oudit

Potential locations of new health care facilities for high risk diabetic kidney clusters in Alberta

Labib Imran Faruque, Bharati Ayyalasomayajula, Rick Pelletier, Scott Klarenbach, Brenda R. Hemmelgarn, Marcello Tonelli
Supervisor: Dr. Marcello Tonelli

INTRODUCTION

Patients with chronic illnesses live far from medical specialists, which may compromise their care. New clinic locations in remote regions are often chosen arbitrarily or based on unproven assumptions about local disease burden. Therefore, the objective of our study was to use the spatial distribution of Alberta patients with both chronic kidney disease (CKD) and diabetes – and to objectively assess the optimal locations for new clinics to serve remote-dwellers.

METHODS

We used data from the Alberta Kidney Disease Network and Alberta Health. We enrolled prevalent Alberta patients (2002-2008) with stage 3-4 CKD and concomitant diabetes with an estimated glomerular filtration rate (eGFR) of 15-59.9 ml/min/1.73m2. We then used two methods to select new clinic locations: plots showing the unadjusted density of patients/100 km2; and SaTScan analysis presenting the prevalent clusters of patients based on CKD rates (adjusted for population size). We estimated the proportion of high risk diabetic kidney patients residing within these identified clusters.

RESULTS

Out of 32,278 patients, a substantial number (8%) resided beyond 200 km of existing nephrology clinics. Density plots localized one large cluster of underserved patients. However, combined application of SaTScan technique and buffer analysis permitted us to detect additional clusters in the northwest and southeast regions of Alberta. The proportions of patients with a hospitalization during follow-up (median 978 days) were higher among patients residing in the newly identified four remote clusters compared to those residing within 50 km of existing nephrology clinics (68%, 69%, 71% and 76% compared to 60%, all $p<0.05$).

CONCLUSIONS

We identified clusters of prevalent remote-dwellers with diabetes and CKD. The higher likelihood of hospitalization in this people reflects the opportunity to use new facilities to improve care. These findings will facilitate evidence-based decision making about new clinic locations in underserved communities. These methods could be used for other disease populations in Alberta.

Supervisor: Dr. Marcello Tonelli

Symptomatic Graft Failure and Impact on Clinical Outcomes after Coronary Artery Bypass Grafting Surgery: Results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Registry

Shavadia J., Graham M.M., Norris C., MacArthur R., Bainey K.R
Supervisor: Dr Kevin Bainey

INTRODUCTION
Introduction: Despite advances in surgical techniques, graft failure (GF) rates post coronary artery bypass grafting (CABG) surgery continue to be high. The association between GF and clinical outcome is however unclear. We sought to identify the prevalence, characteristics and clinical outcomes of symptomatic GF within one year post CABG.

METHODS
Methods: Using APPROACH, a clinical data collection and outcomes initiative capturing all patients undergoing cardiac surgery in Edmonton, Alberta, we identified a cohort of patients undergoing isolated CABG from 2002-2011 who subsequently required repeat coronary angiography within one year. Patient characteristics, indication for angiography, graft failure rate and clinical outcome were prospectively evaluated.

RESULTS
Results: Of 5276 patients undergoing CABG, 5.3% (n=281) required repeat coronary angiography within one year. Of these patients, acute coronary syndrome 64.7% (n=182) was the most common reason for repeat coronary angiography. At angiography, 75.1% (n=211) had GF [internal mammary artery (IMA) 24.9%, saphenous vein graft (SVG) 50.2%]. GF was felt to be the culprit for presentation in 68% (n=191) of cases. Repeat revascularization occurred in 43.4% (n=122), with percutaneous coronary intervention (PCI) to bypass grafts in 14.9% (n=42) and native vessels in 29.5% (n=83). Repeat cardiac surgery was a rare event (3.2%, n=9). Patients with IMA GF had higher long-term mortality (median 6.25 years) compared to patients with SVG GF (adjusted hazard ratio, 2.9; 95% CI 1.27-6.81; p= 0.01).

CONCLUSIONS
Conclusion: Graft failure in symptomatic patients undergoing repeat coronary angiography within one year of CABG remains high. Of particular note is the rate of IMA occlusion, and its association with reduced long-term survival. Further research is required to explore the predictors of GF and its association with adverse outcomes.

Supervisor: Dr Kevin Bainey

Outcomes of Latent Tuberculosis Screening and Therapy in Transplant Recipients Over a 10 Year Period

Aman Sidhu, Geetika Verma, Deepali Kumar, Atul Humar
Supervisor: Dr. D. Kumar, Dr. G. Verma

INTRODUCTION

Pre-transplant screening and therapy of latent tuberculosis infection (LTBI) is recommended. However, tolerability data on LTBI therapy pre- and post-transplant is limited. We studied the tolerability of LTBI therapy and effectiveness of a centralized LTBI treatment program in a low risk population.

METHODS

We retrospectively reviewed provincial TB and transplant databases for all pre- and post-transplant referrals for LTBI therapy over a 10 year period. All eligible patients received therapy with isoniazid and/or rifampin. We examined factors associated with failure to complete therapy and followed patients for active TB.

RESULTS

From 2001-2010, 461 transplant candidates were referred to the TB program for consideration of LTBI screening or therapy. Of these, 200 (43.4%) were eligible for therapy. LTBI was diagnosed based on a positive tuberculin skin test (TST) (n=182), positive QFT-TB (n=1), abnormal CXR (n=13), and clinical assessment (n=4). Both TST and QFT-TB were performed in 23 patients, with concordant results in 16/23. Eleven patients refused therapy. The remaining patients (n=189) were initially prescribed isoniazid (73%), rifampin (12.7%), or another regimen (14.3%). Adequate LTBI therapy occurred in 122 (64.6%). The most common reasons for early discontinuation of therapy were liver enzyme elevation (9.5%), other drug toxicity (13.2%), and death (6.3%). Completion of LTBI therapy was less likely in patients with underlying liver disease (36.9% vs 73.4%; $p<0.001$) and in patients that started therapy post-transplant (51.1% vs 69.0%; $p=0.034$). Liver enzyme elevation was also more likely to occur in those with underlying liver disease (28.3% vs 3.5%; $p<0.001$) and patients that started therapy post-transplant (19.1% vs 6.3%; $p=0.019$). In 599.4 patient-years of follow-up post-transplant (mean 4.9 yrs/patient), there were no cases of active TB.

CONCLUSIONS

A centralized referral program for LTBI therapy in transplant candidates is effective to prevent TB reactivation post-transplant. However, a significant proportion of patients with liver disease do not tolerate standard LTBI therapy. Alternative therapies for these patients should be evaluated.

Supervisor: Dr. D. Kumar, Dr. G. Verma

Differences in Mortality Outcomes among Status Aboriginal Patients and Caucasian Patients with Heart Failure

Lyons KJ, Ezekowitz JA, Liu W, McAlister FA, Kaul P
Supervisor: Dr. Padma Kaul

INTRODUCTION

Status Aboriginal patients have high rates of diabetes and cardiovascular disease predisposing them to the development of heart failure (HF). Whether long-term mortality outcomes among Aboriginal patients differ from those of Caucasian patients with HF is not known. Objectives: To compare 1-year (yr) and 5-yr mortality rates among Aboriginal and Caucasian patients hospitalized with HF.

METHODS

Our population consisted of all Albertans aged ≥ 20 years with an incident HF hospitalization between 2000 and 2008. Vital status as of 12/31/2009 was available for all patients. Aboriginal status was determined by band membership status recorded in the Alberta Health Care Insurance Registry. Caucasian patients were identified as those who were neither Aboriginal, nor of any other major ethnic origin. Logistic regression was used to examine 1-yr and 5-yr mortality after adjustment for baseline variables.

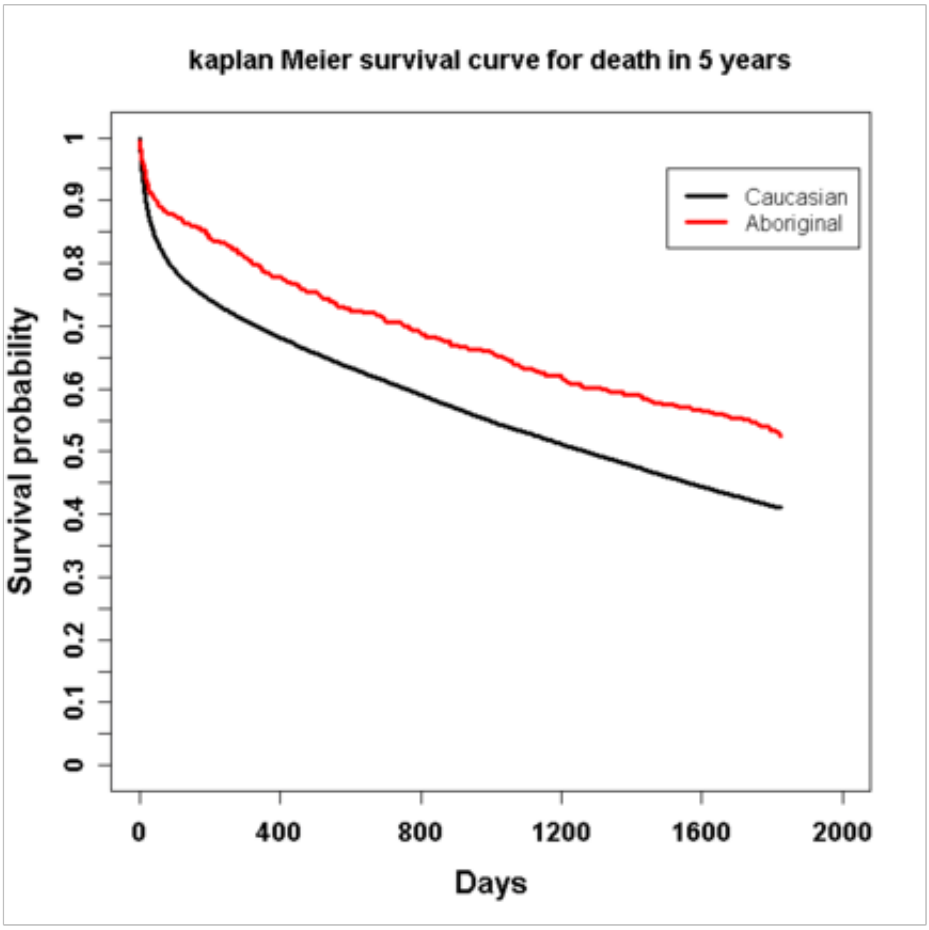
RESULTS

Compared to Caucasians (n=42288), Aboriginal patients (n=1158) were younger at onset of HF (mean age 62.6 vs. 75.4 years, $p<0.001$), had higher rates of diabetes and chronic obstructive pulmonary disease, and lower rates of ischemic heart disease, hypertension, cerebrovascular disease, peripheral vascular disease and atrial fibrillation. Unadjusted 1-yr mortality rates were 22% in Aboriginal and 31% in Caucasians patients ($p<0.01$) but adjusted rates were similar (adjusted Odds Ratio (aOR) 1.09 95% Confidence Interval (CI) 0.89 to 1.34). In the subset of patients from whom 5-yr follow-up data were available (621 Aboriginal and 24537 Caucasians), unadjusted 5-yr mortality rates were 48% in Aboriginal and 59% in Caucasian patients (Figure, $p<0.01$); but after adjustment Aboriginal patients had a 30% higher risk of 5-yr mortality (aOR 1.32, 95% CI: 1.10 – 1.58).

CONCLUSIONS

The lower 1-yr unadjusted mortality rates observed among Aboriginal patients may be explained by their younger age at HF incidence. However, their higher long-term mortality risk suggests a need for more vigilant follow-up of these high-risk patients.

Supervisor: Dr. Padma Kaul


kaplan Meier survival curve for death in 5 years
Survival probability
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
400
800
1200
1600
2000
Days
Caucasian
Aboriginal

Early programming of obesity-related comorbidities among children born from complicated pregnancies

Rueda-Clausen CF1, Ball GDC2,3, Padwal RS1 & Sharma AM1
Supervisor: Drs Arya Sharma & Raj Padwal

INTRODUCTION

Obesity and dyslipidemia are strongly related to each other and to the early onset and severity of atherosclerosis. The prevalence of dyslipidemia among children with obesity (CWO) is very variable. Our previous studies in animal models suggest that offspring born form complicated pregnancies are more susceptible to develop intra-abdominal adiposity and obesity-induced dyslipidemia. Extrapolating these results, we hypothesize that among CWO those born from complicated pregnancies are more likely to have intra-abdominal adiposity and dyslipidemia early in life.

METHODS

This cross-sectional study included CWO (BMI>p90) referred for pediatric weight management. A lipid score was calculated based on triglycerides, total-, LDL- and 1/HDL-cholesterol (each receiving a score of 0=<p75, 1=p75/90, 2=p90/95, 3=>p95) using pre-established sex/age adjusted cut-off points. Factors associated with higher lipid scores were identified by multiple lineal regression. Prenatal records were reviewed to identify history of pregnancy complications. Association between prenatal antecedents and current comorbidities were explored.

RESULTS

In total, 303 CWO were included (46% male; 12.2±2.8 y). After adjusting for BMI, body composition, diet and physical activity; increases in waist/hip ratio (WHR) was associated with higher lipid scores (Coef.5.5 p=0.04). No significant association was observed in blood pressure, glucose homeostasis or any other anthropometric or nutritional parameter. Prenatal records were available in 55 subjects. Prenatal condition associated to fetal hypoxia such as gestational diabetes, preeclampsia, IUGR, and anemia were present in 19 (36%) women. Children born from those complicated pregnancies exhibited a significantly higher WHR than children born from non-complicated pregnancies (0.94±0.01 vs. 0.87±0.01, p=0.01).

CONCLUSIONS

Dyslipidemia in CWO is most strongly associated with central adiposity than BMI or body composition. Among these children, history of pregnancy complication is associated with increased central adiposity. These results reinforce the importance of central adiposity in the early onset of dyslipidemia. Our results also support the effects of pregnancy hypoxic conditions in the future increased susceptibility to central fat distribution.

Supervisor: Drs Arya Sharma & Raj Padwal

Discrepancies in Measures of Left Ventricular Size by Diameter and Volume with Contrast Echocardiography

Patrick Gibson, Peter Wood, Harald Becher, Jonathan Choy
Supervisor: Dr Jonathan Choy

INTRODUCTION

Left ventricular (LV) size is commonly assessed at echocardiography by measurement of the end-diastolic diameter (EDD) in the parasternal long axis view. However, this has recognized limitations, and volumetric measurement from apical views is considered superior, particularly with the use of echocardiographic contrast to improve endocardial border definition. We sought to determine the agreement in classification of LV size by these different measures in a large population of patients undergoing clinically indicated echocardiography.

METHODS

Data were analyzed retrospectively from consecutive patients (n=2008, 61% male, age 62±13 years) who received echocardiographic contrast for LV opacification over 3 years in a single institution. Repeat studies were not included. LVEDD was measured, and LV end-diastolic volume (LVEDV) calculated using Simpson's biplane method. Both measures were indexed to body surface area (BSA) and categorized according to ASE guidelines as normal, mild, moderate or severely dilated.

RESULTS

There was a good overall correlation between LVEDD and LVEDV (Spearman's rho 0.74, $p<0.001$). However, when patients were categorized by indexed (i) LV diameter and volume there was poor agreement in classification (kappa = 0.200). Of 320 patients with severely dilated LVEDVi, only 43 were similarly classified by LVEDDi. Furthermore, 173 patients (54%) with a severely dilated LVEDVi had an LVEDDi in the normal range.

CONCLUSIONS

Agreement between different recommended measures of LV size is limited, even with significant LV dilation. The use of LVEDDi as the sole measure of ventricular size risks under-diagnosing or underestimating the degree of LV dilation. This has implications for reporting in circumstances where accurate assessment of LV size is important, such as timing of surgery in asymptomatic valve disease or classification of cardiomyopathy.

Supervisor: Dr Jonathan Choy

		LV Volume Index (n=2008)			
		Normal	Mild	Moderate	Severe
		n=	n=	n=	n=
LV Diameter Index	Normal	1297	203	126	173
	Mild	16	20	14	69
	Moderate	2	1	4	35
	Severe	1	1	3	43

Systematic review and meta-analysis of bleeding outcomes stratified by gender in venous thromboembolism patients treated with novel oral anticoagulants

Ghazi Alotaibi, Sean McMurtry, Padma Kaul, Cynthia Wu
Supervisor: Dr. Cynthia Wu

INTRODUCTION
Studies performed on acute coronary syndrome patients treated with antithrombotic therapy have shown that women tend to bleed more than men. Whether similar gender differences exist for bleeding from new oral anticoagulants (NOACs) is unknown. We hypothesized women bleed more than men when treated for venous thromboembolism with NOACs, and tested this hypothesis by systematic review and meta-analysis.

METHODS
MEDLINE, EMBASE and Cochrane Library were searched from inception to January 2012. We included trials that randomly assigned participants to receive new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) versus standard of care or placebo for venous thromboembolism. Outcomes were recurrent VTE events and major bleeding. The random effects model was used to pool results. We used relative risks (RRs) to summarize dichotomous results and quantified statistical heterogeneity using the I2 statistic.

RESULTS
We included 13 studies comprising 23558 patients with median age of 57.5 years treated for PE, DVT or both. Forty-three percent were women. Seven studies reported gender stratification for efficacy and five for safety. There was no difference in recurrent VTE between genders [RR 0.97, 95% CI: 0.71-1.33]. We found women on NOACs had more bleeding events than men [RR 0.79, 95% CI 0.66-0.95]. Similar results were observed among men and women given placebo [RR 0.48, 95% CI: 0.24-0.95]. In the standard of care arm (LMWH/VKA), there was a trend toward more bleeding in women [RR 0.85, 95% CI: 0.71-0.1.02, p = 0.09]. However, the standard of care arm was underpowered to show statistical significance (β = 45.1%).

CONCLUSIONS
Women bleed more than men when treated with NOACs for VTE. Its clinical significance requires further investigation and future studies should report outcomes stratified by gender.

Supervisor: Dr. Cynthia Wu

Macrophage Transcripts ADAMDEC1, CXCL13 and CCL18 Selectively Identify T Cell-Mediated Rejection in Humans

Dina F. Badr , Luis G. Hidalgo , Konrad S. Famulski and Philip F. Halloran
Supervisor: Dr. Philip F. Halloran

INTRODUCTION

T cell-mediated rejection (TCMR) is the most common type of rejection in the early post-transplant period. Although macrophages and T cells are the dominant cells infiltrating rejecting allografts, the immune mechanisms unique to this type or rejection are incompletely understood.

METHODS

We examined 403 kidney transplant biopsies for clinical indication (BFC) with diagnoses classified using a modified Banff classification. Using microarray analysis, we compared the gene expression in biopsies with TCMR (n=35) to those with antibody-mediated rejection (ABMR) (n=75) and defined transcripts that are preferentially expressed in TCMR. We studied their relationship to Banff lesions and macrophage/T cell gene expression burdens.

RESULTS

CXCL13, ADAMDEC1 and CCL18 were the top three transcripts with higher expression in TCMR over ABMR as well as when compared to biopsies with no major abnormalities, acute kidney injury, borderline rejection or interstitial fibrosis and tubular atrophy (FDR<0.0001). Correlations between all three transcripts and Banff interstitial inflammation (i-score), tubulitis (t-score) and intimal arteritis (v-score) were also high across all 403 BFC (table 1). Higher expression of ADAMDEC1, CXCL13 and CCL18 was associated with increased T cell/macrophage burden in all 403 BFC and in TCMR biopsies. In a primary human cell panel, expression of these three transcripts was mainly restricted to macrophages.

CONCLUSIONS

Thus expression of macrophage transcripts ADAMDEC1, CXCL13 and CCL18 distinguish TCMR from other Banff categories. Their correlations to Banff lesions associated with TCMR and to the T cell/macrophage burden suggest a role for macrophages in alloimmune mechanisms implicated in TCMR. Better understanding of the role of macrophages in rejecting kidneys may offer helpful diagnostic tools as well as possible future therapeutic targets.

Supervisor: Dr. Philip F. Halloran

Table 1. Correlations of ADAMDEC1, CXCL13 and CCL18 to Banff scores and burdens of macrophages and T cells in 403 BFC †

Probe set ID	Gene	Banff lesion score			T cell burden	Macrophage burden
		i-score	t-score	v-score		
206134_at	ADAMDEC1	0.44	0.40	0.27	0.72	0.78
205242_at	CXCL13	0.37	0.39	0.21	0.74	0.53
32128_at	CCL18	0.30	0.28	0.22	0.48	0.58

† Spearman correlation coefficient, p values <0.0001

Tilt Table Testing in the Evaluation of Neurogenic Syncope: Effect of Increased Duration of Incline.

Derrick Blackmore, BSc; Zaeem A. Siddiqi, MD, PhD
Supervisor: Zaeem A. Siddiqi MD, PhD

INTRODUCTION
Introduction: Neurogenic syncope is primarily diagnosed with drug-free Head-Up Tilt Table Test (HUTT) in autonomic laboratories. The duration of HUTT varies between 10 to 60 minutes among various laboratories though the effect of extended testing time beyond 10 minutes on diagnostic yield remains poorly studied. The purpose of this study was the assessment of the sensitivity of HUTT in the assessment of neurogenic syncope as a function of time.

METHODS
Methods: The HUTT results of patients suspected to have autonomic dysfunction and/or neurogenic syncope referred to the University of Alberta Autonomic Lab were reviewed and positive tests defined as the patient having experienced a syncopal or near-syncopal episode (symptomatic BP drop of >30 mmHg from baseline) were selected for further review. The time to pre-syncope and syncope were noted, as were associated cardiovascular measures.

RESULTS
Results: A total of 334 short duration HUTT (10minutes) and 147 one hour HUTT were performed. A total, of 50 prolonged HUTT resulted in faints or near faints. Among these 50 patients (17 males, 33 females; mean age 38 years), 12 (24%) experienced pre-syncope and/or syncope within 10 minutes; 28 (56%) after 15 minutes of tilt, 36 (72%) at 20 minutes, 40 (80%) at 30 minutes and at 45 minutes 49 (98%). None of the 334 short duration HUTT were positive.

CONCLUSIONS
Conclusions: As a screening tool for neurogenic syncope, HUTT has improved sensitivity with increased duration of tilt. In the presence of an appropriate history of pre-syncopal and syncopal symptoms, a one hour tilt table test is recommended.

Supervisor: Dr. Zaeem A. Siddiqi MD, PhD

Influence of IL-25 on Human Th2 Lymphocyte Differentiation

Graeme Bredo, Alexis Adams, Jessica Storie and Lisa Cameron
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 cells highly express the IL-25 receptor (IL-25R). IL-25 is produced by the epithelium in response to virus, parasite, and antigen, possibly contributing to the initiation of Th2 immune responses. In a mouse model in which 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 naive human CD4 T cells with αCD3/αCD28 and IL-2 in Th2 conditions (IL-4, αIL-12 and αIFNγ) in the presence of either IL-4, IL-25, both or neither cytokine. Proteins were detected by flow cytometry or ELISA. qRT-PCR was used to assay mRNA expression.

RESULTS

Comparison of mRNA levels of freshly isolated CD4 T cells and CRTh2+ Th2 cells using microarray analysis, showed a 300-fold increase for IL-25R in Th2 cells ($p<0.05$), which was substantiated by qRT-PCR. Cells differentiated in the presence of IL-4 or IL-25 alone expressed higher intracellular IL-4 compared to neither cytokine ($p<0.05$). Furthermore, additive effects were observed on intracellular IL-4 and are developing on surface CRTh2 and intracellular GATA3. IL-25 was also associated with increased IL-5 and IL-13 protein ($p<0.05$).

CONCLUSIONS

These findings show abundant IL-25R expression on CRTh2+ Th2 cells and stimulation through IL-25R induces Th2 effector cytokines. In addition, IL-25 increases intracellular IL-4 both independent of and additively with IL-4.

Supervisor: Dr. Lisa Cameron

Iron-overload cardiomyopathy is driven by oxidative stress mediated Ca2+ cycling defects leading to selective diastolic dysfunction: prevention with resveratrol dietary intervention

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Supervisor: Dr.Gavin Y.Oudit

INTRODUCTION

Iron-overloaded cardiomyopathy is a newly recognized cause of heart failure with high morbidity and mortality at international scale. Iron-induced oxidative stress leading to selective diastolic dysfunction is associated with genetic (primary hemochromatosis) as well as acquired (secondary iron-overload) conditions.

METHODS

Iron-overload cardiomyopathy was induced by treating 10 week old male C57Bl6 mice sub-acutely with iron-dextran at 5 mg/25g body weight i.p, 5 days/week for 4 weeks. The antioxidant and metabolic modulator, resveratrol was given at 190 mg/kg/day in the regular diet.

RESULTS

Quantification of tissue iron showed significant deposition in the heart (350±27vs 5304±773 µg/mg tissue; n=10, $p<0.01$) which was confirmed by Prussian blue staining. Hemodynamic (+dP/dt/-dP/dtmax ratio=1.0±0.05vs 1.7±0.07; n=6) and echocardiographic (E/A ratio: 1.46±0.04vs 1.27±0.06, n=6, $p<0.05$; E'/A' ratio: 0.77±0.04vs 1.20±0.05, n=7, $p<0.01$) analysis showed diastolic dysfunction with preserved systolic function in iron-overload hearts in the absence of increased myocardial fibrosis. Resveratrol treatment prevented the development of diastolic dysfunction (E/A ratio: 1.27±0.06vs 1.67±0.13 and E'/A':1.2±0.05vs 0.80±0.02; n=7, $p<0.01$; hemodynamic: +dP/dt/-dP/dt ratio: 1.6±0.14vs 1.1±0.09; n=6, $p<0.01$) without altering the degree of iron-overload. Increased expression of disease markers, ANF (65%), BNP (103%) and β-MHC (44%) were normalized with resveratrol treatment. Expression of oxidative stress-related genes, thioredoxin (91%), catalase (140%), glutathione peroxidase (548%) and superoxide dismutase (87%) were increased in iron-overloaded hearts treated with resveratrol resulting in normalization of reduced glutathione (GSH: 50±18.49vs 250±56.65ng/mg tissue). Ca2+ transients in isolated cardiomyocytes were slowed with decreased SERCA2a (50%) and increased NCX1 (65%) protein levels, respectively, which were normalized by resveratrol treatment

CONCLUSIONS

Iron-overload resulted in oxidative stress mediated abnormal Ca2+cycling dependent selective diastolic dysfunction with preserved systolic function. Treatment of iron-overload cardiomyopathy with resveratrol can prevent oxidative stress in myocardial tissues and protect the heart from progression to diastolic heart failure.

The Effect of 1,25-Dihydroxyvitamin D3 on the In Vitro Viability of Peripheral Blood Eosinophils from Allergic/Asthmatics

Caroline Ethier, Francis Davoine
Supervisor: Dr. Francis Davoine

INTRODUCTION

Epidemiological studies correlate vitamin D deficiency with asthma severity. Dendritic and lung epithelial cells hydroxylate vitamin D precursors into its physiologically active form, calcitriol (1,25 dihydroxyvitamin D3) in vitro. Also, calcitriol modulates receptor and cytokine expression from various leukocytes in an anti-inflammatory manner. Little is known about the direct effect of calcitriol on eosinophils, despite their role in allergy. We hypothesize that calcitriol will exert direct immunomodulatory effects on eosinophils through its apoptotic pathway.

METHODS

Peripheral blood eosinophils from atopic donors were isolated and incubated with calcitriol and anti-apoptotic factors. A dose response was completed using physiological concentrations of calcitriol (0 to 100 nM). The additive effect of calcitriol and Interleukin-5 (IL-5), at 1ng/mL, and Interferon-γ (IFNγ), at 100 ng/mL, was investigated on a 14 and 7 day time course, respectively. Viability levels were measured using Annexin-V and PI staining by flow cytometry.

RESULTS

Calcitriol (10nM) sustained eosinophil viability similar to IL-5 (1ng/mL) after 24 hours. In contrast, calcitriol only treatment yielded only (4.47 ± 1.49%, n = 12) viability after 7 days compared to control media (2.13 ± 2.13%, n = 12). Co-incubation with IL-5 and calcitriol increased viability (86.44 ± 1.51%, n = 12) compared to IL-5 alone on day 7 (65.97±2.38%, n = 12) which indicates a synergistic effect of calcitriol on IL-5 sustained eosinophil viability.

CONCLUSIONS

Calcitriol is an immunoregulator of eosinophil viability by potentiating the anti-apoptotic effects of IL-5. Sustaining eosinophil viability might decrease cytotoxic mediator shedding in mucosa from necrotic eosinophils, therefore reducing mucosal inflammation.

Supervisor: Dr. Francis Davoine

Akt1 Inhibition Negatively Regulates Endothelial Cells Angiogenesis, Migration and Adhesion in Vitro.

Maikel Farhan and Allan G. Murray
Supervisor: Dr. Allan Murray

INTRODUCTION

Angiogenesis is the formation of new blood vessels from existing ones. Angiogenic tumor neovascularization is targeted in adjuvant regimes for a variety of cancers via inhibition of Vascular Endothelial Growth Factor (VEGF) signaling in the endothelial cells (EC). VEGF stimulation of EC recruits a variety of signal transduction pathways, including phosphoinositide 3- kinase (PI3K) and the downstream kinase Akt. However, the molecular mechanism(s) that mediate Akt-dependent matrix invasion by angiogenic EC are poorly defined. Here we investigate if Akt1 regulates EC interaction with matrix molecules in vitro.

METHODS

Using RNA interference, we studied the effect of Akt1-loss in EC: we compared Akt1-deficient cells to non-silenced cells for angiogenic invasion into a 3D fibrin matrix, migration and protrusion formation in 2D scratch wound-healing assay. To evaluate the effect of Akt1 loss on matrix adhesion, we used Electric Cell-substrate Impedance Sensing and direct cell counting after replating.

RESULTS

We lowered Akt1 expression to less than 40% in EC using two different siRNA. Akt1-deficient cells remained viable. Akt1 deficiency inhibited 3D angiogenic sprouting by 60%±8% (mean±SEM; $P<0.05$) vs control siRNA-treated cells. In 2D, Akt1-deficient cells migrated 24%±5.5 (mean±SEM; $P<0.05$) slower than the wild type cells. Similarly, early protrusions of Akt1-deficient EC were attenuated by 39%±2% (mean±SEM; $P<0.05$). Further, integrin alpha5/ beta1-mediated adhesion of EC to either gelatin or fibronectin, was reduced in Akt1-deficient EC vs non-silenced cells to 45%±11% or 39%±8% (mean±SEM; $P<0.05$), respectively.

CONCLUSIONS

Taken together, this data shows that Akt1 in EC regulates angiogenesis and migration in vitro in part by controlling cell adhesion to matrix. As a pro-survival pathway often dysregulated in tumors, the PI3K/Akt pathway is targeted for cancer cell chemotherapy. Our data suggests Akt1 is also a potential target to inhibit cancer neovascularization.

Supervisor: Dr. Allan Murray

PROTEINASE ACTIVATED RECEPTOR-2 REGULATION ON AIRWAY EPITHELIUM

Gandhi V and Vliagoftis H
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Proteinase Activated Receptor -2 (PAR-2), a G-protein receptor, is involved in inflammatory reactions in many organs. PAR-2 activation on airway epithelial cells leads to the release of inflammatory mediators. PAR-2 polymorphisms have been linked with asthma and PAR-2 expression is increased on the airway epithelium of asthmatics compared to control subjects. PAR-2 may be an airway epithelial cell sensor for allergens with serine proteinase activity, such as cockroach, house dust mite and fungal allergens, but also for endogenous proteinases released during allergic inflammation. However, PAR-2 regulation on airway epithelium is poorly understood. Since asthmatic airways are under stress from hypoxia and/or inflammation, we hypothesized that cellular stress and in particular inflammatory stimuli are responsible for PAR-2 upregulation.

METHODS

To study the role of inflammatory stimuli on PAR-2 expression, we treated Normal Human Bronchial Epithelial (NHBE) cells with PAR-2 activating peptide (AP) and inflammatory mediators IL-4, IL-13, histamine and IFN-γ. Moreover to evaluate the effects of cellular stress on PAR-2 expression, cells were subjected to starvation by using media without any growth factors. PAR-2 expression was studied by qRT-PCR and western blotting 2-24 h after treatment.

RESULTS

PAR-2 activation and studied inflammatory mediators had no effect on PAR-2 expression. Cellular stress showed significant 2.6 +/- 0.2 and 2.2 +/- 0.2 fold upregulation (n=5) of PAR-2 mRNA at 6h and 24h, respectively. Addition of epinephrine inhibited stress induced PAR-2 upregulation (n=3).

CONCLUSIONS

Stress upregulated PAR-2 mRNA, but it does not appear to be through inflammation as the studied inflammatory mediators had no effect on PAR-2 expression. Cellular stress could be the mediator of PAR-2 upregulation in asthmatic airways. Adrenergic receptor activation may neutralize stress effects. Understanding the mechanisms of these effects could lead to the development of more specific treatments for preventing PAR-2 mediated airway inflammation.

Supervisor: Dr. Harissios Vliagoftis

Endothelial expression of the PI 3-kinase catalytic isoform p110 beta is required for sprouting angiogenesis and kidney microvascular repair

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Supervisor: Dr. Allan Murray

INTRODUCTION

Angiogenesis is a complex process that requires coordination of multiple cell types, and activation of multiple signaling pathways. PI3 kinase catalytic isoforms integrate many of these signals downstream of tyrosine kinase and G-protein coupled receptors, but the role of individual isoforms in repair of the established vasculature is unclear. Whereas endothelial expression of the p110 alpha catalytic isoform is critically required for embryonic vascular development, we sought to determine if the p110 beta isoform participates in repair of the adult microvasculature.

METHODS

In vitro, we studied the effect of p110 beta siRNA knockdown (k/d) on sprouting angiogenesis of human late blood outgrowth endothelial progenitors (hEPC) into a 3-D fibrin gel. In vivo, we investigated the role of p110 beta during vascular assembly by hEPCs, and vascular repair in the kidney after glomerular endothelial cell (GEC)-selective injury induced in Tie2ERT2Cre/p110βflox/flox mice.

RESULTS

Loss of p110 beta reduced hEPC sprouting and the length of sprout extension. This correlated with decreased expression of tip cell markers DLL4 and apelin but not ESM1, and was associated with a reduction in hEPC migration and proliferation. In vivo, vasculogenesis using p110 beta-deficient hEPC showed a reduction of capillary–like structures versus control hEPC. Further, the conditional knockout of p110 beta in the mature mouse vascular endothelium impaired repair after GEC injury. The endothelial p110 beta-deficient mice had higher serum creatinine and urea concentration, and suffered early death compared to control animals.

CONCLUSIONS

These results demonstrate an important role for endothelial p110 beta in angiogenic sprouting in vitro, and assembly of human EC into vascular structures in vivo. Further, loss of endothelial p110 beta expression in the mouse impairs repair of the renal microvasculature following injury.

Supervisor: Dr. Allan Murray

Physician and Patient Knowledge of Reproductive Issues in Inflammatory Bowel Disease is Highly Variable

Vivian W. Huang, Karen I Kroeker, Karen Goodman, Kathleen Hegadoren, Levinus A. Dieleman, Richard N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Inflammatory bowel disease (IBD) often affects patients in their early adulthood years. Studies have shown a high rate of voluntary childlessness in women with IBD. It is unclear what knowledge and beliefs lead IBD patients to voluntary childlessness. The aims of this study were to assess 1) female IBD patient knowledge and beliefs, and 2) physician knowledge and practice patterns, regarding reproductive issues in IBD.

METHODS

Female IBD patients (18-45yr) were prospectively identified through a university clinical database. Patients were sent questionnaires: 1) demographics 2) reproductive history 3) reproductive beliefs 4) Crohn's and colitis pregnancy knowledge (CCPKnow) score (poor (0-7) adequate (8-10) good (11-13) very good (14-18)). Physicians attending GI conferences, referring physicians, and members of the Canadian Association of Gastroenterology were invited to complete the CCPKnow, and a questionnaire regarding practice patterns. Mean scores were compared using student t-test or ANOVA.

RESULTS

The patient response rate was 32% (109/338), and for physicians 22% (145/670). The mean CCPKnow score among patients was 7.5+4.5. The CCPKnow score was higher in patients who discussed family planning with their gastroenterologist than those who did not (9.5+3.7 vs 5.3+4.3, $p<0.001$). 26% of patients were concerned about passing IBD to their child; 32% believed pregnancy would worsen their disease; and 25% were concerned of IBD medications causing birth defects.

GI trainees and gastroenterologists, 15.6+2.0, 17.0+1.6, respectively, had higher CCPKnow scores than general practitioners, 10.3+3.9 ($p<0.001$). There were significant deficits in physician knowledge of medications in the reproductive period, some of which are harmful in pregnancy.

CONCLUSIONS

Female IBD patients have barely adequate knowledge and significantly varied beliefs regarding the effect of IBD on pregnancy. General practitioners have limited knowledge regarding reproductive issues in IBD compared to specialists or GI trainees. Despite good knowledge, gastroenterologists have widely varied practices regarding the management of pregnant IBD patients.

Supervisor: Dr. Richard Fedorak

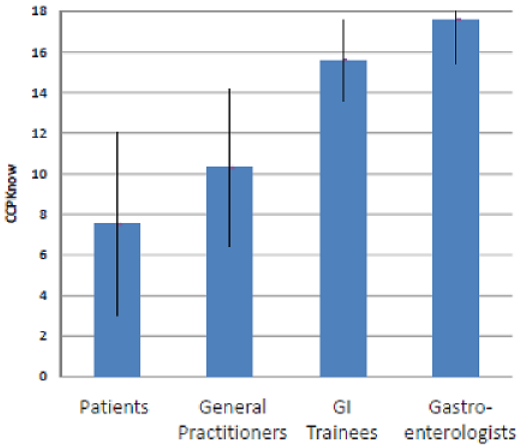

Figure 1. CCPKnow scores increase from patient to specialist.

A Functional Nuclear Pyruvate Dehydrogenase Complex is Important for a Mitochondrial-Independent Generation of Acetyl-CoA and Histone Acetylation

Adam Kinnaird, Gopinath Sutendra, Peter Dromparis, and Evangelos D. 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 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 either glucose or pyruvate, resulting in decreased S-phase entry. Pyruvate dehydrogenase kinase, which inhibits PDC, was not detectable in nuclei, and its induction resulted in serine-293 phosphorylation of the E1α component of mitochondrial, but not nuclear PDC, suggesting differential regulation. Epidermal growth factor signaling increased nuclear localization of PDC.

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

Chemically defined diet alters the protective properties of fructo-oligosaccharides and isomalto-oligosaccharides in a rodent model of colitis

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Supervisor: Dr. Levinus Dieleman

INTRODUCTION

Dysbiosis of intestinal microbiota is important for the pathogenesis of inflammatory bowel diseases. The composition and metabolic activity of gut microbiota can be modified by different environmental factors such as diet. Feeding fructo-oligosaccharides (FOS) and isomalto-oligosaccharides (IMO) in HLA-B27 transgenic rats changed specific cecal microbiota, associated with reduction of colitis, but their protective mechanisms remained unclear. The aim of this study was to examine if feeding a purified AIN-76A diet versus a standard rat chow diet, supplemented with or without FOS or IMO, can modify the effects of these prebiotics on colitis development and intestinal microbiota.

METHODS

HLA-B27 transgenic rats were fed AIN-76A diet or chow diet supplemented with IMO, FOS or not for 12 weeks. Intestinal inflammation was assessed by quantifying mucosal IL-1β and microscopic colitis. Cecal contents were analyzed for specific microbiota composition using quantitative PCR as well as for short chain fatty acids (SCFA).

RESULTS

Both fibers failed to reduce colitis in the presence of AIN-76A diet compared to transgenic animals fed chow diet. Quantification of dominant bacterial groups showed that numbers of bifidobacteria and Enterobacteriaceae were stimulated by FOS versus control and IMO treatment regardless of the background diet. Chow diet rather than prebiotic treatments, mediated a significant increase of numbers of clostridial clusters XI and XIVa, as well as butyrate-kinase compared to rats on AIN-76A diet. Higher concentration of total SCFA were observed in cecal contents of rats on chow compared to the purified diet. AIN-76A diet increased the relative proportions of propionate, and branched-SCFA irrespectively the prebiotic treatment.

CONCLUSIONS

Changes in the bacterial composition induced by prebiotics did not mediate protection from colitis development when purified diet was used. Although diet modifies cecal microbiota, our study indicates that bacterial metabolites rather than the specific composition of intestinal microbiota are associated with colitis reduction.

Supervisor: Dr. Levinus Dieleman

PrPC modulates A-type K+ currents through Dipeptidyl Aminopeptidase-like protein 6

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Supervisor: Dr. David Westaway

INTRODUCTION

The cellular prion protein (PrPC) is broadly expressed in the adult central nervous system and associated with a variety of processes including neuronal excitability. Dipeptidyl aminopeptidase-like protein 6 (DPP6) was first identified as a PrPC interactor using in vivo formaldehyde crosslinking of wild type (wt) mouse brain.

METHODS

crosslinking, molecular biology, electrophysiology, microscopy

RESULTS

This interaction was confirmed in three heterologous cell lines and because DPP6 directs the functional assembly of voltage gated K+ channels, we assessed PrPC's impact upon Kv4.2-based cell-surface macromolecular complexes. Wt PrPC modulates Kv4.2 channel properties causing an increase in peak amplitude, rightward shift of the voltage-dependent steady-state inactivation curve, slower inactivation and a faster recovery from steady-state inactivation. This effect upon A-type voltage gated K+ channels occurs only in the presence of DPP6. Contrasting with wt PrPC, a Gerstmann-Sträussler-Scheinker disease version of PrP with eight extra octarepeats exhibited loss-of-function both for complex formation and for modulation of Kv4.2 channels.

CONCLUSIONS

This interaction may may influence the heightened vulnerability to drug-induced seizures observed in Prnp0/0 mice as well as implicate the regulation of Kv4.2 channels by PrPC as a mechanism that could potentially contribute to the PrPC dependent effects of oligomeric Aβ assemblies.

Supervisor: Dr. David Westaway

Hypoxia Results In Upregulation And De novo Activation Of Von Willebrand Factor Expression In Lung Endothelial Cells

Anahita Mojiri, Maryam Nakhaii-Nejad, Wei-Lee Phan, Stephen Kulak, Aneta Radziwon-Balicka, Paul Jurasz, Evangelos Michelakis, Nadia Jahroudi
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Von Willebrand Factor (VWF) is an endothelial specific prothrombotic molecule, and exclusively expressed in endothelial cells (EC) and megakaryocytes. Its increased levels in lung are associated with diseases such as pulmonary hypertension (PH). The objective of our study is to determine the mechanism of increased VWF levels in conditions such as hypoxia that contribute to PH.

METHODS

We have previously reported generation of transgenic mice that express LacZ transgene under the regulation of lung and brain specific transcriptional regulatory elements of the VWF gene. Hypoxia exposure of these transgenic mice resulted in increased VWF and LacZ mRNA levels as well as redistribution of their expression from primarily larger vessels in the lung to microvessels. Inaddition,to address our objective,ChIp analysis, western-blot and Si-RNA experiments were performed.

RESULTS

Exposure of cultured human lung microvascular EC to hypoxia demonstrated that VWF up regulation was accompanied by increased platelet binding. Transcription upregulation was mediated through inhibition of the repressor NF-IB association with the VWF promoter, increased nuclear translocation of YY1, and increased association of YY1 with its cognate binding site on the lung-specific regulatory region of the VWF gene. Knockdown of YY1 expression abolished the hypoxia-induced upregulation of the VWF and platelet chain formation on the surface of endothelial monolayer .

CONCLUSIONS

These analyses demonstrate that hypoxia induces a procoagulant shift to lung microvascular endothelial cells leading to increased platelet adhesion. Transcriptional upregulation of VWF gene is mediated through modulation of NF-IB and YY1 activities. NF-IB and YY1 may independently be targets of hypoxia and contribute to VWF upregulation. Alternatively, the close proximity of these two negative and positive regulators of the VWF promoter through chromatin looping may influence binding activity of one by another, specifically increased YY1 binding may interfere with the repressor NF-IB binding to the VWF promoter.

Supervisor: Dr. Nadia Jahroudi

TIMAP is Critical for Endothelial Cell proliferation, survival and Angiogenesis

Marya Obeidat,Laiji Li and Barbara Ballermann
Supervisor: Dr. Barbara Ballermann

INTRODUCTION

Angiogenesis, the process of new blood vessel formation from pre-existing vessels, is vital for embryonic development, wound healing and tumor vascularization. Angiogenic sprouts elongate through EC proliferation. TIMAP is an EC-predominant protein phosphatase 1 regulatory subunit, highly expressed in developing blood vessels. Here, we show that TIMAP depletion significantly inhibits EC proliferation, survival and angiogenesis through inhibition of the Akt pathway.

METHODS

To deplete TIMAP, glomerular EC were transfected with TIMAP-specific siRNA. Control EC were transfected with nonspecific siRNA. DNA synthesis was evaluated by EdU incorporation. The time-dependent increase of electrical impedance across the EC monolayers was used as a measure of EC proliferation. Activation of EC apoptosis was examined by western blot analysis of cleaved caspase 3, and fluorometric quantification of caspase 3 activity. To study angiogenesis, confluent EC monolayers on collagen-coated beads were embedded in fibrin gels followed by quantification of sprouts. Levels of total and phosphorylated proteins in EC lysates were determined on Western blots by LiCor Odyssey imaging. Results are expressed as mean ± SEM.

RESULTS

Compared to control EC, TIMAP depletion reduced EdU incorporation 38.2 ± 1.9% ($P < 0.05$, $n = 3$) and the rate of electrical impedance development by 93% ± 1.7% ($p < 0.05$, $n=4$). Cleaved caspase 3 and caspase 3 activity were much higher in TIMAP depleted, than in control cells. TIMAP depletion decreased angiogenic sprouts by 43 ± 1.3% compared to control EC ($p < 0.05$, $n=3$). TIMAP depletion profoundly reduced serum-stimulated Akt phosphorylation on T308 and S473 (- 83 ± 0.2%, $p < 0.01$, $n=4$), without affecting the total Akt or ERK1/2 phosphorylation.

CONCLUSIONS

TIMAP is required for angiogenesis, at least in vitro. It is permissive for EC proliferation and inhibits apoptosis. These effects are dependent on activation of the Akt, but not the ERK1/2 MAPK pathway.

Supervisor: Dr. Barbara Ballermann

Colectomy Rates for Medically-Refractory Ulcerative Colitis Have Declined in Parallel with Increasing Anti-TNF Use

Krista M. Reich, Richard N. Fedorak, MD, Karen J. Goodman, PhD, Haili Wang, MD, Levinus A Dieleman, MD, Karen I. Kroeker, MD
Supervisor: Dr. Karen Kroeker

INTRODUCTION

Ulcerative colitis (UC) can be treated by surgical removal of the large intestine. Surgery, however, can be deemed less attractive due to the overall impact on patients' quality of life. Medical therapy remains the mainstay treatment for UC, with surgery reserved for medically-refractory disease. The advent of cyclosporine and anti-TNF therapy in the UC algorithm for medically-refractory disease has extended medical management options. Our aims were to determine if colectomy rates for UC have changed since the introduction of cyclosporine and anti-TNF therapy.

METHODS

The Edmonton area health database was used to identify adults who were admitted to one of the four major hospitals with a diagnosis of UC and who underwent a colectomy between January 1, 1998 and December 31, 2011 for medically-refractory disease. The total population of UC cases in the Edmonton area was estimated for each calendar year by multiplying the annual prevalence of UC in Alberta by the annual Edmonton population. Results were presented as percent of UC patients having a colectomy per year.

RESULTS

There were 535 colectomies over the study period. The colectomy rate was 1.7%/year (95% CI: 1.0, 2.6) in 1998, peaked in 2002 (3.1%/year, 95% CI: 2.3, 4.1), and then declined over a 9 year period to 1.3%/year (95% CI: 0.09, 1.8) in 2011 (Figure 1). From 1998-2002, the colectomy rate increased, paralleling the decline in cyclosporine use. Subsequently, the decline in colectomy rate after 2002 paralleled the introduction and utilization of anti-TNF therapy. UC patients who underwent colectomy were further explored by stratifying on emergent or elective indication.

CONCLUSIONS

The rate of colectomy for medically-refractory UC has declined since 2002, and this decline parallels the increase of anti-TNF use in this population. Patients undergoing emergent colectomy have a shorter duration of disease and a longer median length of stay in hospital.

Supervisor: Dr. Karen Kroeker

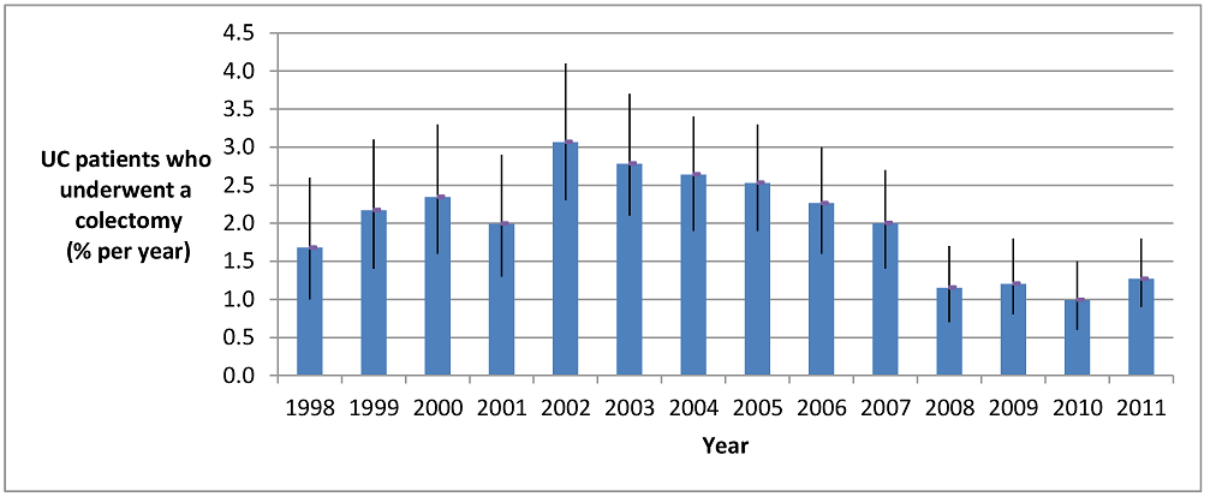


Figure 1. The Average Annual Colectomy Rate Shows A Decreasing Trend Since 2002

In vivo 4.7 Tesla MRI-based manual hippocampal segmentation identifies subfield-specific volume loss in patients with mesial temporal sclerosis: Results from a pilot study

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

INTRODUCTION

Histological literature has demonstrated that classical mesial temporal sclerosis (MTS)selectively involves certain hippocampal subfields (CA1&CA4) and spares others (CA2+/-CA3). Studies have indicated that atypical subtypes of MTS (CA1 predominant &endfolium sclerosis) have different responses to temporal lobectomy. Thus, methods to identify subfield-specific volume loss could assist in predicting surgical outcome preoperatively. Our group has described a method for in-vivo manual segmentation of the human hippocampus in healthy controls. We aimed to determine if this technique identifies subfield-specific volume loss in patients with MTS.

METHODS

Four healthy volunteers aged 23-56 and four unilateral-temporal lobe epilepsy (TLE) patients (based on telemetry) aged 26-45 were studied. TLE patients were classified as MTS(3/4) vs. nonlesional (NL)(1/4) based on quantitative T2 relaxometry. All subjects were scanned at 4.7T using a T2-weighted Fast Spin Echo sequence (spatial resolution 0.52x0.68x1.0mm3). Hippocampi were segmented and subfield volumes measured for the: A) DG(Cornu-Ammonis-4 and Dentate-Gyrus) B)SUB(Subiculum) C) CA(Cornu-Ammonis-1-3). Patient volumes were compared to the lower limit of normal (calculated as normal controls´ mean volume(n=8) minus two standard-deviations).

RESULTS

Volume loss was identified in the DG subfield in 1/3 MTS patients contralateral to the symptomatic hippocampus, while all other subfields were spared. In the symptomatic hippocampus, significant volume loss was demonstrated in 2/3 patients. One patient demonstrated atrophy of CA and DG, while the other manifested volume loss in all three subfields. The single nonlesional patient did not manifest volume loss in either hippocampus.

CONCLUSIONS

Our preliminary results suggest that hippocampal subfield pathology can be detected with subfield volumetry performed using high resolution MRI at ultrahigh magnetic field strength. These preliminary observations require confirmation with larger sample size. In addition, histological validation of in vivo segmentation protocols is required.

Supervisor: Dr. Donald Gross

Potential role of insulin-like growth factor-II receptor in amyloid precursor protein processing

Yanlin Wang 1,2; Satyabrata Kar 1,2,3
Supervisor: Dr. Satyabrata Kar

INTRODUCTION

The insulin-like growth factor-II (IGF-II) receptor involves in the transport of newly synthesized lysosomal enzymes from the trans-Golgi network to endosomes. The endosomal-lysosomal system, the major site of IGF-II receptor expression, plays a critical role in the processing of amyloid precursor protein (APP) leading to the generation of β-amyloid (Aβ) peptide - a key player in the development of Alzheimer's disease pathology. However, the role of IGF-II receptor in APP processing remains unclear. To address this issue we used IGF-II receptor overexpressing and deficient fibroblast cell lines to study the influence of the receptor on APP processing and Aβ metabolism.

METHODS

IGF-II receptor overexpressing and deficient cells were cultured in DMEM and then processed using AD-PCR-arrays to detect the mRNA levels of markers of APP processing. Western blotting, fluorometric kits and ELISA were used to measure levels of APP, its processing enzymes and Aβ. Confocal microscopy and lipid raft isolation were used to detect the distribution of the receptor, APP and its processing enzymes. IGF-II receptor knockdown by siRNA was used to verify these findings.

RESULTS

PCR-array data revealed higher mRNA levels of APP as well as β- and γ-secretases in IGF-II receptor overexpressing cells. In accordance with PCR-array data, we observed increased levels of APP, Aβ immediate precursor proteins and activities of β- and γ-secretases in IGF-II receptor overexpressing cells. Secreted N-terminal APP fragment, Aβ1-40 and Aβ1-42 were higher in their conditioned media. These changes can be reversed by knocking down the receptor levels. Additionally, higher levels APP and its processing enzymes colocalized with IGF-II receptors were detected on lipid raft which is an active site of APP processing.

CONCLUSIONS

Higher levels of IGF-II receptors increase APP level and processing possibly at cholesterol rich membrane domain leading to enhanced production of Aβ-related peptides.

Supervisor: Dr. Satyabrata Kar

3D Echocardiography in a Dynamic Heart Phantom: Challenging the Contour Finding Algorithm in an Abnormally Shaped Ventricle

Wood, P and Becher, H
Supervisor: Prof Harald Becher

INTRODUCTION

Semi-automated contour finding algorithms have been introduced in order to facilitate and shorten processing of three-dimensional (3D) echocardiographic datasets. Validation has been performed mainly in cohorts of patients with ellipsoid shaped ventricles. A new dynamic heart phantom provides ventricular volumes with normal and abnormal shapes. We sought to investigate the ability of a commercially available semi-automated algorithm to measure left ventricular (LV) volumes and represent the true ventricular chamber shape and volume compared to the known values.

METHODS

3D datasets were obtained from a mechanically driven heart phantom (Shelley Medical Imaging Technologies) using a commercially available 3D echocardiography scanner (IE33, Philips Inc.). Two independent observers (reader 1 and 2) analysed the recordings using 3 different approaches: A1 - semi-automated volumetric method without manual correction, A2 - manual correction of the initial contour, A3 - manual correction of the final contour. The volume measurements were compared with the true volumes of the phantom.

RESULTS

In ventricular volumes with ellipsoid and asymmetric, abnormal shapes there was excellent agreement of volume measurements between both readers using Bland Altman method (bias±1.96 SD = -0.59mL±3.2mL, -0.54mL±3.2). In the abnormally shaped ventricles there were considerable differences between multiple measurements in different 3D datasets using all automated methods. Compared to the true volumes method A1 resulted in an underestimation of up to 20.2ml (32% of the true volume), average 18.5% ± 2.8%. With manual correction (A2 and A3) the maximum underestimation of the true volume was 12.8%.

CONCLUSIONS

All semi-automated contour finding programs showed limitations in finding the endocardial contour and providing an accurate volume assessment in an abnormally shaped ventricle. There is a considerable variability in measurements of an abnormal LV volume which is probably due to the inability to optimise the alignment of the long axis length of the LV.

Supervisor: Dr. Prof Harald Becher

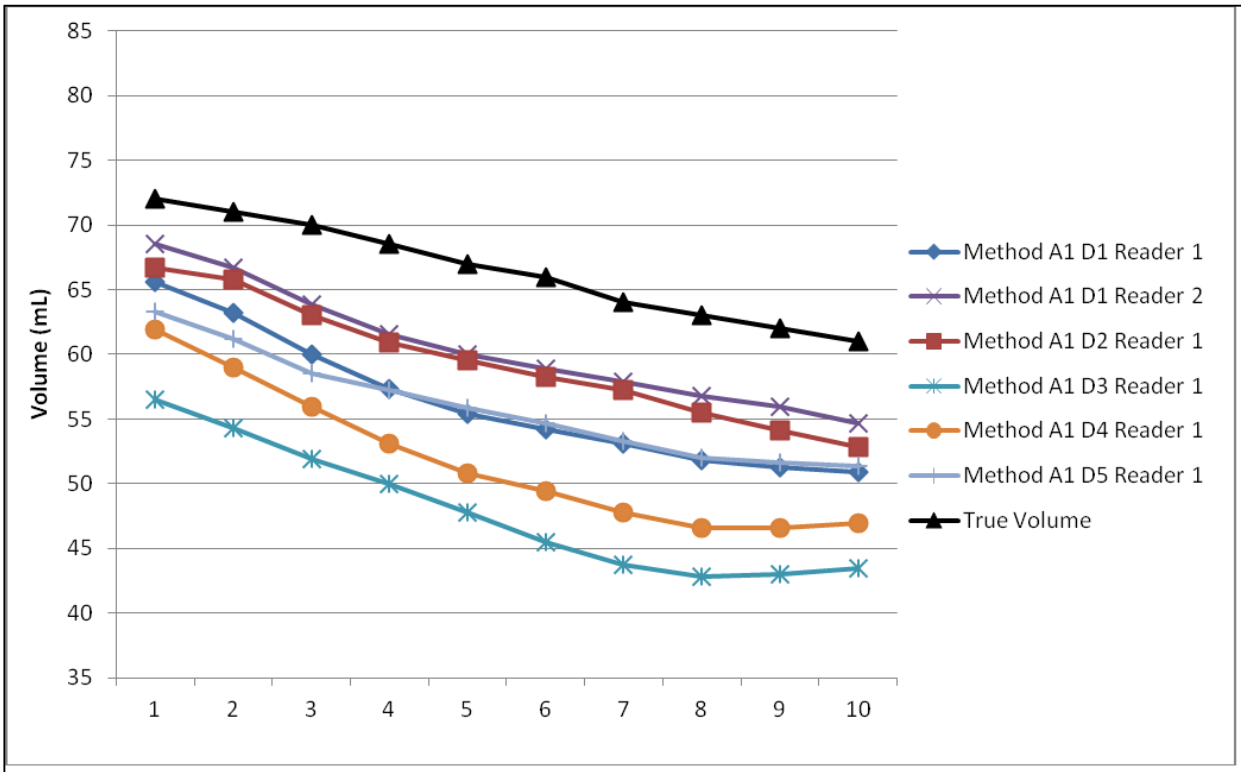


Figure1. Comparison of method A1 with the true volumes and two readers. Method A1 = semi-automated volumetric method with no manual correction; D1 = Dataset 1; D2 = Dataset 2; D3 = Dataset 3; D4 = Dataset 4; D5 = Dataset 5.

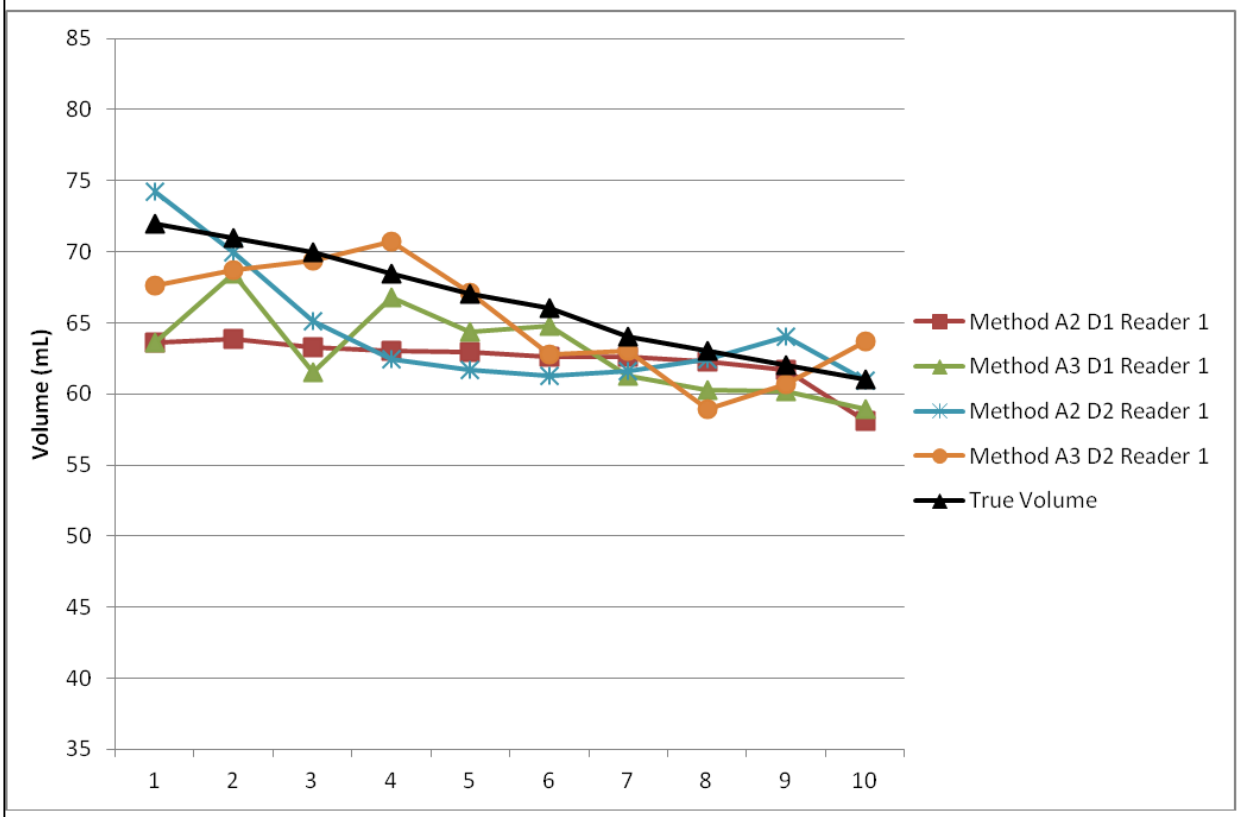


Figure 2. Comparison of methods A2 and A3 with the true volumes. Method A2 = semi-automated volumetric method with pre-processing manual correction; Method A3 = semi-automated volumetric method with post-processing manual correction; Method C = Simpsons Biplane Method of Discs; D1 =

An Improved Method to Assess Post-Transplant Kidney Function

R Al-Sehli(1), SO Grebe(2), Z Jacaj(1), S Wen(1), S Shua-Lin(1), S Yilmaz(3), VA Luyckx(1), TF Mueller(1)
Supervisor: Dr.Thomas Mueller

INTRODUCTION

Routine monitoring of kidney transplant function relies almost exclusively on serum creatinine measurements. However, this ignores the impact of donor nephron supply and recipient demand. We developed a method to calculate the difference between expected and observed transplant function as a new measure to assess kidney transplant performance. We propose that this method will better detect the performance difference between living and deceased donor transplants. Transplant literature supports the superior outcome of living Vs deceased donor transplants.

METHODS

We developed a formula to express the expected kidney function (exp GFR) by integrating donor and recipient age, weight, gender, creatinine and renal adaptive capacity. The individual exp GFR was then calculated for recipients of 79 living (LD) and 67 deceased donor (DD) kidneys. These recipients were followed for a mean period of 70 ±16 months and their observed kidney function (obs GFR) was assessed at day 7, month 3, years 1,3,4 and 5. The percent difference between obs GFR and exp GFR [Δ% (exp GFR-obs GFR) was used to express the functional variation between LD and DD transplants

RESULTS

Donor (D) and recipient (R) demographics were similar between the LD and DD groups at time of transplantation. When Kidney transplant function was only assessed by serum creatinine and estimated GFR formulas (Cockroft-Gault , MDRD and CKD-Epi) , we observed no difference in function between LD and DD transplants. As shown on table.1,the difference in performance was only demonstrated when Δ% (exp GFR-obs GFR) was calculated. This finding supports the fact that LD transplants have a superior outcome compared to DD transplants.

CONCLUSIONS

Integration of donor and recipient anthropometric parameters to calculate the expected kidney transplant function represents a new method for assessment of post transplant function.

Supervisor: Dr.Thomas Mueller

	D-Cr[µmol/l]	obs GFR Y1 [ml/min]	obs GFR Y4 [ml/min]	Exp GFR [ml/min]	Δ%(exp GFR-obs GFR) Y1	Δ%(exp GFR-obs GFR) Y4
LD [n=79]	72	71	72	76	1	15
DD [n=67]	68	73	76	92	13	-3
P value	n.s	n.s	n.s	0.0042	0.053	0.011

Table 1. Δ%(expected GFR-observed GFR) Vs. observed GFR . D-Cr, donor creatinine; obs GFR Y1, observed GFR at year 1 post transplant; obs GFR Y4, observed GFR at year 4 post transplant; Exp GFR, expected GFR in the recipient.

Effects of Protease-Activated Receptor 2 (PAR2) blockade in a chronic model of allergic airway inflammation and remodeling

Muhammad Asaduzzaman, Courtney Davidson and Harissios Vliagoftis
Supervisor: Harissios Vliagoftis

INTRODUCTION

Protease-Activated Receptor 2 (PAR2) is a G protein-coupled receptor activated by serine proteinases. PAR2 activation is associated with inflammation. We have previously shown that PAR2 activation in the airways mediates allergic sensitization to various inhaled allergens and is involved in the development of acute allergic inflammation and airway hyperresponsiveness (AHR) in murine systems. We now hypothesize that functional inhibition of PAR2 prevents allergic inflammation, AHR and measures of remodeling in chronic allergic airway inflammation models.

METHODS

BALB/c mice were sensitized with 8 intranasal (i.n.) administrations of CE over 2 weeks. Animals were then challenged with the same allergen for 2 consecutive days in every 2 weeks for a total of 6 rounds. To investigate the role of PAR2 in the development of AHR and airway inflammation we administered a blocking anti-PAR2 monoclonal antibody (SAM-11) or an isotype matched control antibody i.n. before every challenge with CE. A control group received saline only. AHR, airway inflammation, serum IgG1 and hydroxyproline levels in the lungs were assessed 24h after the last challenge with CE.

RESULTS

Mice sensitized and challenged with CE developed AHR, and showed increased accumulation of eosinophils in bronchoalveolar lavage (BAL) and collagen content in the lung tissue, and increased levels of CE-specific IgG1 in serum compared to saline controls. Administration of the SAM-11 significantly inhibited all parameters induced by CE.

CONCLUSIONS

Our data demonstrate that PAR2 signaling constitutes a key role in CE-induced AHR and airway inflammation/remodeling in mice also in chronic settings. These findings suggest that targeting PAR2 activation may lead to a new therapeutic strategy for allergic asthma.

Supervisor: Dr. Harissios Vliagoftis

Incremental health care costs associated with multidisciplinary chronic kidney disease care

Betty Chui, Brenda Hemmelgarn, Braden Manns, Marcello Tonelli, Scott Klarenbach
Supervisor: Scott Klarenbach

INTRODUCTION

Multidisciplinary chronic kidney disease (MCKD) care is commonly provided, however its impact on health care costs in a real world setting is not clear. This study compares incremental health care costs in CKD patients receiving and not receiving MCKD care.

METHODS

From 2002 to 2007, all incident CKD patients with two consecutive eGFR measurements < 45 mls/min/m2 at least 90 days apart were identified and tracked for patient level costs from a population based cohort in Alberta over 5 years. Patients who initiated dialysis within 90 days, or who had pre-emptive or subsequent transplant after dialysis were excluded. Incremental mean health care costs associated with MCKD care were estimated using adjusted multivariable linear regression models for patients who did and did not initiate dialysis during the study period.

RESULTS

For CKD patients who did not initiate dialysis during the study period, there were no significant differences in adjusted total health care costs comparing patients cared in or outside of a MCKD clinic (Table 1), although MCKD was associated with higher drug costs ($975). For CKD patients who initiated dialysis, MCKD care was associated with a significant decrease in total health care costs in the year prior to dialysis initiation of $14,019, driven by significantly decreased hospitalization costs of $12,227.

CONCLUSIONS

For CKD patients who initiate dialysis, MCKD care is associated with significantly decreased total health care costs in the year prior to dialysis initiation. This data can be used to inform optimal provision of MCKD.

Supervisor: Dr. Scott Klarenbach

Table 1: Adjusted Total and Categorical Mean Health Care Costs fo

	Control (n)	MCKD (n)	**Adjusted Total Costs – CKD**	**Adjusted Incremental Cost of MCKD**	**Adjuste** Physicia fees
CKD Only Group Annual Costs	36,625	653	15,541	1,070	
Dialysis Group Pre dialysis year 2	1,169	443	16,920	23	
Pre-dialysis year 1	1,178	443	48,569	**-14,019**	
Incident dialysis year	995	424	73,451	-212	
Subsequent Post Dialysis Years	573	315	56,506	2,801	

***Bolded values are statistically significant at the 5% level**

Association between self-reported adherence to a low-sodium diet and sodium-related dietary behavior among chronic heart failure patients.

Eloisa Colin-Ramirez, Finlay McAlister, Elizabeth Woo, Nellie Wong, Justin Ezekowitz
Supervisor: Dr. Justin Ezekowitz

INTRODUCTION

Despite the importance of a low-sodium diet in HF patients, compliance with this dietary intervention continues to be an issue. Therefore, there is a need to better understand the potential barriers perceived by the patients, which in turn might help provide guidance to improve adherence. The main objective of this study was to evaluate self-perception of compliance with a low-sodium diet and dietary behaviours in chronic heart failure patients.

METHODS

Methods: This study was based on a dietary questionnaire completed routinely from all the patients attending the Heart Function Clinic at the Mazankowski Alberta Heart Institute. Patients were divided into three groups according to the degree of self-reported adherence to a low-sodium diet: Never, Sometimes and Always. The questionnaire additionally asked about intake of high-sodium processed food.

RESULTS

A total of 237 patients (median age = 65.6 years, 72.6% male) were included. Patients that stated Always following a low-sodium diet were less likely to use salt in cooking or at the table, compared to the other two groups. However, 4.2% of the patients in the Always group reported eating canned or package soups every day. The highest proportion of patients eating fast foods 1-3 times/week was found among those who stated Sometimes following a low-sodium diet (22.9%) compared with Never (9.1%) and Always (6.7%, p=0.002). The Sometimes patients also tended to more frequently eat processed meat, compared to the Never or Always following a low-sodium diet groups (p=0.09). The rest of the food items did not show any significant differences between groups.

CONCLUSIONS

HF patients associate the idea of following a low-sodium diet mainly with avoiding salt in cooking or at the table, but not with reducing frequency of intake of high-sodium processed food. Creative education methods, reinforcement and surveillance are needed in order to identify and correct misconceptions regarding a low-sodium diet.

Supervisor: Dr. Justin Ezekowitz

The long-term effects of dietary sodium restriction on clinical outcomes in patients with heart failure: SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure)

Eloisa Colin-Ramirez, Finlay McAlister, Gary Newton, JoAnne Arcand, Sean Virani, Paul Armstrong, Justin Ezekowitz
Supervisor: Dr. Justin Ezekowitz

INTRODUCTION

Heart failure (HF) remains one of the most common, disabling, expensive and fatal medical conditions. Importantly, many urgent clinical visits, emergency department visits and acute-care hospitalizations are linked to dietary salt indiscretion. The primary nutritional strategies in HF patients are focused on sodium reduction to minimize the risk of acute volume overload episodes. However, there is a lack of data to support this strategy and thus there is no consensus among guidelines regarding the recommended level of dietary sodium intake for patients with chronic HF. Current recommendations on sodium restriction vary from <2000 mg to 3000 mg. The main objective of this study is to evaluate the long-term effects of a low-sodium diet vs. a moderate-sodium diet on composite clinical outcomes (CV hospitalizations or ED visits, all-cause mortality) in patients with chronic HF.

METHODS

A multicenter, open-label, blinded adjudicated endpoints, randomized controlled trial in 1000 ambulatory patients with chronic HF to evaluate the efficacy of a low sodium diet compared to a moderate sodium diet on clinical outcomes. The total duration of the trial is 12 months. Intervention: Patients will be randomized to one of two levels of sodium restriction: low (1500 mg/d) or moderate-sodium diet (2300 mg/d). Patients in both groups will receive sample menus to guide their meal plan. These menus will be in accordance with the energy requirement and level of sodium restriction for each patient. Also, patients in both groups will receive conventional pharmacological and non-pharmacologic treatment for HF, and will be advised to adjust their fluid intake as per current guidelines. Patients will be contacted monthly by phone, and every 3 months in person for reinforcement of the diet with 3-day food records used to assess adherence.

RESULTS

Study is currently ongoing as a pilot study at the UofA hospital and 38 patients has been enrolled.

CONCLUSIONS

None

Supervisor: Dr. Justin Ezekowitz

Effect of low-dose dopamine on cardio-respiratory physiology in heart failure patients

Heather Edgell, M. Sean McMurtry, Ian Paterson, Justin A. Ezekowitz, Mark J. Haykowsky, Jason R.B. Dyck, Michael K. Stickland
Supervisor: Dr. Michael Stickland

INTRODUCTION

Previous work has shown that carotid chemoreceptor (CC) inhibition increases cardiac output at rest in dogs with heart failure (HF).

METHODS

To translate this knowledge to humans, we recruited clinically stable HF patients (n=7; EF: 36±15%) and risk-matched controls (CON; n=9; EF: 64±4%) from the Heart Function Clinic at the University of Alberta hospital, the Alberta HEART study, and from the general population. Ventilation, blood pressure, ECG, and aortic ultrasound were measured. Dopamine (DA) was infused at 2µg/min/kg to inhibit the CC.

RESULTS

At rest, we found higher mean arterial pressure (98±14 vs 78±9mmHg; p=0.003) and higher total peripheral resistance index in CON (0.05±0.03 vs 0.04±0.01mmHg/mL/min/m2; p=0.01). These differences could be due to more frequent anti-hypertensive treatment in HF. The DA decreased ventilation in HF (7.6±2.1 vs 6.8±1.7L/min; p=0.04) but not in CON (6.7±2.0 vs 6.7±2.0L/min; p=0.96). While there was no difference in cardiac output index (Q) at rest between groups (p=0.15), after DA infusion HF patients had higher Q (CON:1.7±0.5 vs HF:2.6±0.5L/min/m2; p=0.02).

CONCLUSIONS

In HF, low-dose DA inhibits the CC and increases resting cardiac performance.
Funded by Heart and Stroke Foundation of Canada.

Supervisor: Dr. Michael Stickland

The influence of strategic D-amino acid substitution on amyloid beta 14-23 aggregation

Jitendra Kumar and Valerie Sim
Supervisor: Dr. Valerie Sim

INTRODUCTION

Alzheimer's Disease is the most common cause of dementia; the aggregation of the peptide Aβ (1-42) is fundamental to its pathogenesis. Aβ 14-23 is one of the smallest self-assembly sequences within the Aβ peptide. Within this region, residues 17-21 have been identified as sites for self-adhesion. Furthermore, structural data from Aβ fibrils suggest that phenylalanine (Phe) at positions 19 and 20 are part of the amyloid core. Benzene rings from Phe 19 and 20 form intermolecular stacks and therefore may stabilize Aβ fibrils. We hypothesized that D-amino acid substitution of these Phe within the 14-23 peptide might produce a peptide able to: 1) selectively and diagnostically bind the disease-associated forms of Aβ; 2) block Aβ self-assembly; and / or 3) weaken or alter self-assembly, producing non-toxic or easily degraded forms of Aβ aggregate.

METHODS

We synthesised Aβ 14-23 peptides with D-Phe at substituted at position 19 and/or position 20 using a Liberty1 peptide synthesiser. Peptides were purified using a c-18 column on a Gilson HPLC. Aggregation reactions were performed by incubating full length Aβ peptide (1-42) with the synthesized peptides in PBS at 37°C and monitoring aggregation by Thioflavin T (ThT) fluorescence. Toxicities of the peptides and aggregate species were determined by MTT assay in cell culture. Structural characteristics were determined using light scattering and electron microscopy.

RESULTS

Peptide 14-23 is known to readily form ThT positive aggregates. The peptides with substitutions at position 19 alone significantly altered aggregation tendencies of Aβ (1-42) and showed higher orders of aggregation. In contrast, substitution at position 20 reduced the rate of Abeta aggregation. Toxicity and structural profiles are presented.

CONCLUSIONS

Subtle chemical modification of single Phe residues in the Aβ 14-23 peptide completely abolishes the self-aggregation of this peptide. These altered peptides, in turn, dramatically influence the aggregation profile of Aβ (1-42).

Supervisor: Dr. Valerie Sim

Preclinical down-regulation of PrPC precursor suggests a fundamental mechanism for the slow progression of prion infections.

Charles E. Mays1, Chae Kim2,3, Tracy Haldiman2, Jacques van der Merwe1, Agnes Lau1, Michele A. Di Bari4, Umberto Agrimi4, Qingzhong Kong2,3, Jan Langeveld5, Debbie McKenzie1,6, David Westaway1,7,8, and Jiri G. Safar2,3
Supervisor: David Westaway

INTRODUCTION

Prion diseases are invariably fatal neurodegenerative disorders typically associated with extended incubation periods that can last for up to decades. In attempt to explain the characteristic incubation periods of these disorders, we hypothesized that PrPC was down-regulated preclinically as we have previously observed for the PrP-like Shadoo protein.

METHODS

To test this hypothesis, PrPC was specifically analyzed during prion infection by separating it from disease-associated PrP species using sucrose gradient fractionation in conjunction with conformation dependent immunoassays. Additionally, the scrapie cell assay was utilized to estimate infectivity of our samples, while PMCA was implicated to recapitulate in vivo conditions for PrPSc replication.

RESULTS

We found that PrPC is reduced quantitatively in cultured cells supporting prion propation, preclinically in mouse-adapted scrapie models, as well as at endpoint in rodent models used to study scrapie, Creutzfeldt-Jakob disease, and chronic wasting disease. Moreover, PrPC was altered qualitatively by the disease process in terms of its glycotype profile.

CONCLUSIONS

These findings imply that a generalized host defence mechanism affecting both PrPC and Shadoo is activated during prion disease. Since PrPC is the essential substrate required for PrPSc replication and toxic signaling, down-regulation likely contributes to the extended sub-clinical phase associated with prion infections.

Supervisor: Dr. David Westaway

Angiotensin II Induced Proteolytic Cleavage of Angiotensin Converting Enzyme 2 is mediated via the TNF-alpha Converting Enzyme (TACE/ADAM-17): A Positive Feedback Mechanism in the RAS

Vaibhav B. Patel1,2, Nicola E. Clarke3, Zuocheng Wang1,2, Brendan Putko1,2, Jennifer Lo1,2, Anthony J. Turner3 and Gavin Y. Oudit1,2,4
Supervisor: Dr. Gavin Y. Oudit

INTRODUCTION

Introduction: 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. Ang II regulates TNFα Converting Enzyme (TACE) activity via differential cellular compartmentalization. We hypothesize that Ang II suppresses ACE2 by increasing TACE activity and ACE2 cleavage, thereby exacerbating its pathological effects via a positive feedback mechanism.

METHODS

Wildtype (WT) mice were infused with Ang II (1.5 mg/kg/day) for 2 weeks.

RESULTS

Ang II infusion in WT mice for 2 weeks resulted in substantial decrease in myocardial ACE2 protein levels and activity with corresponding increase in plasma ACE2 activity. Irbesartan, an AT1 receptor blocker, prevented the Ang II induced loss of cardiac ACE2. Ang II infusion also resulted in AT1R mediated substantial increase in myocardial TACE expression and activity. Spatial co-localization between TACE and ACE2 in the heart revealed a direct interaction between TACE and ACE2 at the membrane level. Ang II treatment in HuH7 cells exhibited AT1R dependent metalloproteinase mediated shedding of ACE2 while transfection with siTACE (100 nM) suppressed TACE levels and prevented Ang II stimulated shedding of ACE2. p47phoxKO mice showed were resistant to Ang II-induced reactive oxygen species formation in association with preservation of myocardial ACE2 levels leading to reduced Ang II-induced cardiac dysfunction and hypertrophy suggesting that oxidative stress is an activator of TACE. We found increased plasma ACE2 activity in patients with systolic heart failure with reduced and increased membrane-associated ACE2 and TACE, respectively, in explanted failing human hearts.

CONCLUSIONS

Our data illustrate that Ang II induces ACE2 shedding by promoting TACE activity as a positive feedback mechanism whereby Ang II facilitates the loss of its negative regulator, ACE2. In heart failure, where plasma Ang II levels are elevated, elevated plasma ACE2 activity likely represents loss of the protective effects of ACE2 in the tissues including the heart.

Supervisor: Dr. Gavin Y. Oudit

A miR-208-Mef2 axis drives the decompensation of right ventricular function in Pulmonary Hypertension.

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

INTRODUCTION

Right Ventricular Failure (RVF) is the major cause of morbidity and mortality in pulmonary hypertension (PHT) but remains understudied compared to left ventricular failure (LVF). The transition from a compensated (CRV) to decompensated (DRV) stage occurs much earlier in the RV for unknown reasons. RV and LV have a different embryologic origin; the Islet1/Myocyte enhancer factor 2 (Mef2)/Hand2 axis is specific for RV formation. Mef2 has been implicated in the regulation of metabolic, contractile and angiogenic genes critical for RV adaptation to pressure overload. MicroRNAs (miRNAs) have emerged as important determinants of LV development and disease, but little is known about RV miRNAs. We hypothesized that a miRNA-Mef2 axis is driving the transition from CRV to DRV.

METHODS

We studied free RV wall tissue from rats with normal RV function (NRV, RVSP=38±2mmHg, CO=102±2ml/min and RV/LV+Septum=22±1), CRV (RVSP=66±8 mmHg, CO=80±13ml/min, RV/LV+Septum=48±3, 3-4weeks post-monocrotaline) and DRV (RVSP=52±2mmHg, CO=67±10ml/min, RV/LV+Septum=58±2, ascites, weight loss, 4-6weeks post-monocrotaline) (n=6 in each group).

RESULTS

Using miRNA arrays (n=9), we found that the levels of cardiac specific miRNA miR-208 progressively decreased in CRV and DRV, correlating with failure progression ($r=-0.68$, $n=20$, $p<0.001$); whereas its expression is known to remain stable in models of LV pressure overload hypertrophy. The level of the miR-208 target, MED13, is increased in DRV. MED13, a subunit of the complex mediator of transcription, has been associated with the repression of several metabolic genes through the activation the repressor NCoR1. NCoR1 is known to deacetylate Mef2 family members, decreasing their transcriptional activity. NCoR1 expression was increased in DRV, while Mef2 expression was decreased. We infected adult cardiomyocytes isolated from CRV free walls with an adenovirus expressing an anti-miR-208. This was associated with increased MED13 and NCoR1 levels, and decreased Mef2 expression, mimicking the transition to DRV in vivo.

CONCLUSIONS

We identified a miR-208-Mef2 axis characterizing the transition from CRV to DRV.

Supervisor: Dr. Evangelos D. Michelakis

Targeting ER stress with chemical chaperones as a novel therapeutic strategy in idiopathic pulmonary fibrosis (IPF).

Roxane Paulin, Peter Dromparis, Lavinia Ionescu, Andrew Qi, Gopinath Sutendra, Bernard Thebaud and Evangelos D. Michelakis.
Supervisor: Dr. Evangelos D. Michelakis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, irreversible interstitial lung disease with limited therapeutic options. Disease progression is characterized by aberrant and excessive deposition of a collagen-rich extracellular matrix by activated lung fibroblasts, leading to the destruction of the normal alveolar architecture, reducing lung compliance and compromising gas exchange. Emerging evidence suggests the implication of endoplasmic reticulum stress (ER) and activation of the unfolded protein response (UPR). The UPR is designed to improve protein folding and prevent cell death from accumulation of misfolded proteins that can aggregate and interfere with basic cellular functions. We hypothesized that a chemical chaperone like 4-phenylbutyrate (PBA) that can be used clinically and has been shown to promote protein folding and attenuate UPR in several diseases could be beneficial for IPF.

METHODS

We used in vitro cultured human pulmonary fibroblasts HPFBs, treated or not with bleomycin (1mU/mL/48h) and in vivo the mice model of IPF after intra-tracheal bleomycin injection (4U/kg). PBA was administered in the drinking water (10 days, ≈500mg/kg/day) in a reversal protocol, at day 10 after bleomycin injection.

RESULTS

In HPFBs, bleomycin treatments induced a significant increase in collagen production (western blot (WB) and Sircol assay) and enhanced differentiation of fibroblasts into myo-fibroblasts (actin immunofluorescence (IF)). This was associated with a 2-fold increase in the UPR transcription factor ATF6 activation and expression of its target NOGO (WB/IF). PBA (10uM) reversed those observations in vitro. In vivo, PBA treatments were beneficial by: 1)improving functional capacity (Treadmill, 248.6±63.5m vs 151.7±19.1m), 2)decreasing static and dynamic elastance (flexiVent, 18.8±3 vs 24.9±5, 26.8±4.6 vs 33.1±6 cmH2O.s/mL respectively) 3)improving pressure/volume loops in the lungs 4)decreasing the fibrotic grade (H&E/Ashcroft grade 3.74±0.3 vs 6.25±0.6), and 5)decreasing collagen deposition (Masson-Trichrome).

CONCLUSIONS

Our data suggest that attenuating ER stress by chemical chaperones may be a novel therapeutic strategy for IPF.

Supervisor: Dr. Evangelos D. Michelakis

Validation of the FAt Spondyloarthritis Spine Score (FASSS). A New MRI Scoring Method for the Evaluation of Fat Lesions in the Spine of Patients with Axial Spondyloarthritis

Susanne Juhl Pedersen; Zheng Zhao; Robert GW Lambert; Mikkel Østergaard; Ulrich Weber; Walter P. Maksymowych
Supervisor: Dr. Walter Maksymowych

INTRODUCTION
Fat lesions on MRI of the spine may constitute an important measure of treatment efficacy as well as a surrogate marker for structural damage progression in patients with axial spondyloarthritis (SpA). The aim of this study was to develop and validate a new scoring method for fat lesions in the spine, the FAt SpA Spine Score (FASSS).

METHODS
The fat lesions scored are defined according to anatomical location and are recorded dichotomously (present/absent) at each vertebral endplate. The scoring range per disco-vertebral unit (DVU) for the cervical (C) spine: 0-8, thoracic (T) and lumbar (L) spine: 0-24, resulting in a total score range of 0-456. A reference image set and a web-based online module were developed. Two rheumatologists evaluated MRI scans obtained at two time points (mean 1.5 years (SD 0.5)) in chronological order of 67 patients (exercise 1). Thereafter, scoring methodology and reference images were revised based on discrepant cases. The two readers re-read 30 randomly selected pairs of MRI scans from the first exercise together with 40 new pairs of MRI scans (exercise 2) (mean 1.7 years (SD: 0.8)).

RESULTS
In exercise 2, the change in fat scores ranged from -33 to 48 for reader A and from -38 to 54 for reader B. Inter-observer intra-class correlation coefficients (ICCs) were high to very high for the baseline scores, and improved substantially in change scores from exercise 1 to 2 (Table). Inter-observer ICCs for baseline scores were high for all spinal segments, and change scores improved from small to moderate for the C spine, from moderate to high for the L spine and remained very high for the T spine.

CONCLUSIONS
The FASSS meets essential validation criteria for further assessment in axial SpA, and may thus be useful for follow-up of SpA in clinical trials and practice.

Supervisor: Dr. Walter Maksymowych

Table

Interobserver ICCs for spinal segments scored according to the CanDen Fat SpA Spine Sco

	ICC (CI95%)				
	Exercise 1 (n=67)		Exercise 2 (n=70)		Ex
	Baseline	Change	Baseline	Change	
C spine	0.69 (0.27;0.85)	0.08 (-0.16;0.31)	0.83 (0.74;0.89)	0.40 (0.18;0.58)	0.
T spine	0.86 (0.78;0.91)	0.82 (0.72;0.89)	0.91 (0.84;0.95)	0.88 (0.81;0.92)	0.
L spine	0.77 (0.65;0.86)	0.31 (0.07;0.51)	0.92 (0.88;0.95)	0.83 (0.73;0.89)	0.
Total	0.89 (0.82;0.93)	0.69 (0.53;0.79)	0.95 (0.91;0.97)	0.89 (0.83;0.93)	0.

*The 30 patients, that were scored two times, were a subgroup of patients in exercise 1 and

1H-NMR based metabolomic profiling of Experimental Autoimmune Encephalomyelitis (EAE): a novel approach to understanding Multiple Sclerosis

SN Reinke, DI Broadhurst, and C Power
Supervisor: Christopher Power

INTRODUCTION

Multiple Sclerosis (MS) is a debilitating neurodegenerative disease affecting as many as one in five hundred Canadians. Metabolomics is the systematic study of low molecular weight (bio)chemicals characterizing the convergence of gene expression and environmental stimuli. Experimental Autoimmune Encephalomyelitis (EAE) initiates a T-cell mediated immune response to myelin, thereby mimicking MS; EAE is the most widely used animal model of MS.

HYPOTHESIS: A metabolomic time-course study of central nervous system (CNS) tissue from EAE mice will reveal pathogenic insights into immune system mediated demyelination and identify novel therapeutic targets.

METHODS

C57BL/6J mice were induced with EAE, using Complete Freund’s Adjuvant (CFA), pertussis toxin, and Myelin Oligodendrocyte Glycoprotein (MOG)35-55. Animals were euthanized at 4 time points during disease: 2 days prior to clinical onset, day of onset, post-onset/pre-peak disease, and peak disease. Disease severity was defined by weight and degree of paralysis. Two sets of control mice were also observed at all time-points: (1) healthy controls receiving no induction and (2) CFA controls receiving CFA and pertussis toxin. 1H-NMR metabolomic analyses were performed on spinal cords - the primarily affected CNS tissue.

RESULTS

Univariate data analyses identified several metabolites as being significantly altered in EAE animals; these included energy metabolites (pyruvate, lactate, succinate, fumarate), lipid metabolites (acetylcarnitine, carnitine, choline, phosphocholine), amino acids, and biogenic amines (GABA, N-acetylasparate, myo-inositol, taurine). Changes in energy metabolism were corroborated by molecular analyses. Multivariate data analyses revealed that the spinal cord metabolomes of EAE-induced animals were similar to those of the control groups prior to disease onset. After disease onset, EAE-induced animals had a divergent temporal metabolite trajectory when compared to the two controls groups, which followed similar trajectories.

CONCLUSIONS

These data reveal that the immune-mediated demyelination process is associated with energy metabolism changes, identifying these central pathways as potential therapeutic targets.

Supervisor: Dr. Christopher Power

Ingested Airborne Particulate Matter Alters Neonates' Intestinal Immune Function and Bacterial Handling in IL-10 Deficient Mice

Salim SY (1), Kaplan GG (2), Barkema H (2), Wine E (1), Madsen KL (1)
Supervisor: Dr. Karen L Madsen

INTRODUCTION

Particulate matter (PM) is a key pollutant in ambient air that has been linked with adverse health conditions in urban environments. Incidences of inflammatory bowel diseases (IBD) are highest in developed countries, and most commonly affects children and young adults. Our aim was to study the effect of ingested PM on developing intestine in the IL-10-/- colitis model, and if chronic exposure during the neonatal period would alter disease development and/or have long-lasting effects.

METHODS

IL-10-/- pregnant dams and pups were fed mouse chow with/without PM (9µg/g) and pups were studied at 10, 14 and 20 weeks of age. To examine mucosal immune function, segments of small and large intestines were homogenized for cytokine analysis via MesoScale discovery platform, while homogenates from mesenteric lymph nodes (MLN) were cultured to measure bacterial translocation. Level of serum endotoxin was evaluated using LAL Assay kit. While in vitro assay of bacterial uptake and killing was done using THP-1 cell lines.

RESULTS

PM increased pro-inflammatory cytokines IL-1β, IFNγ and TNFα in small and large intestines of 10 and 14 weeks old mice. This was associated with increased levels of bacterial translocation into MLN. IL-17 levels was reduced by PM in the 10 weeks old mice but was increased at 14 weeks when compared to age-matched controls. The endotoxin levels were significantly higher in all mice fed PM, indicating reduced clearance. This was corroborated by in vitro assay where PM reduced bacterial uptake and killing in THP-1 macrophages.

CONCLUSIONS

IL-10-/- neonatal mice exposed to PM had an increased bacterial translocation, poor bacterial killing and an earlier onset of inflammation. Our data suggest the urban particulate pollution alters both local GI responses and systemic bacterial clearance, possible providing a mechanism for increased inflammatory conditions.

Supervisor: Dr. Karen L Madsen

Increased proportion of CD4+ T cells expressing CRTh2 in severe asthma

Nami Shrestha Palikhe, Drew Nahirney, Cheryl Lane, Harissios Vliagoftis, Lisa Cameron
Supervisor: Dr. Lisa Cameron

INTRODUCTION

Chemoattractant receptor homologous molecule expressed on Th2 cells (CRTh2) is expressed by Th2 cells, eosinophils and basophils. CRTH2 is a receptor for prostaglandin D2 and has been shown to be associated with asthmatic airways disease. Recently, we found a higher percentage of eosinophils, basophils and CD4+ T cells expressing CRTh2 in subjects with allergic airways disease compared to non-allergic controls. Here, we localize the cell type expressing CRTh2 and hypothesize that CRTh2 expression is different according to the severity and phenotype of asthma.

METHODS

Thirty subjects followed by specialists in asthmatic care were prospectively recruited from an outpatient tertiary referral centre in Edmonton, AB, between 2012 and the present. Severe asthma was defined by ATS criteria. Whole blood was analyzed for cellular expression of CRTH2 using flow cytometry. Quantitative real-time PCR measured mRNA expression of CRTh2, IL-4 and IL-13 and the Th2 transcription factor, GATA-3.

RESULTS

Study participants were 43.84 ±2.51 years old, and 53.33 % female. Demographics were similar between mild/moderate and severe asthma. Severe asthmatics exhibited a higher percentage of circulating CD4+CRTh2+ T cells compared to mild/moderate asthmatics (5.26 ± 0.62 vs. 3.34±0.25, $p<0.01$). Similarly, asthmatics on high dose inhaled corticosteroids exhibited a higher percentage of CD4+CRTh2+ T cells, when compared to asthmatics on lower doses (4.57± 0.55 vs. 3.48±0.28, $p<0.05$). A higher proportion of CD4+CRTh2+ T cells was correlated with expression of IL4 ($p<0.05$) mRNA, a Th2 cytokine. Interestingly, there was no difference in the percentage of eosinophils (84.88±4.50 vs. 87.06±3.29) or basophils (71.08±5.12 vs.74.70±8.80) expressing CRTh2 between mild/moderate vs. severe asthma ($p>0.05$).

CONCLUSIONS

CRTh2 is differentially regulated across cell types and CD4+CRTh2+ T cells may contribute to the pathophysiology underlying asthmatic airways disease. Further work is ongoing to determine the relationship between CRTh2 and phenotypes of asthma, and to delineate the role of CRTh2 in this disease process.

Supervisor: Dr. Lisa Cameron

IDENTIFICATION OF PEKIN DUCK INTERFERON LAMBDA-3 AND INITIAL ASSESSMENT OF ITS ANTIVIRAL EFFECTS IN THE DUCK HEPATITIS B MODEL

Yao Q, Fischer KP, Arnesen K, Tyrrell DL and Gutfreund KS
Supervisor: Dr. Klaus Gutfreund

INTRODUCTION

Interferon lambda-3 (IFN-λ3), also known as interleukin-28B (IL-28B), belongs to the recently discovered type III interferons and IL-10 family of cytokines. Type III interferons induce antiviral responses similar to type I interferons but signal through a different heterodimeric receptor complex (IFN-λR1/IL-10R2). IFN-λ3 inhibits replication of many viruses, especially those affecting epithelial cells of the respiratory and gastrointestinal tracts and the liver. The aim of this study was to identify and characterize duck IFN-λ3 (duIFN-λ3) to study its role in the immunopathogenesis of duck hepatitis B virus (DHBV) infection.

METHODS

The duIFN-λ3 cDNA was obtained by RT-PCR and RACE. A homology model of duIFN-λ3 was obtained using the structure of human IFN-λ3 as a template. A eukaryotic expression vector was generated for expression of a C-terminal-His6-tagged IFN-λ3 protein and culture supernatants of transfected 293T cells were assessed by immunoblot using an anti-His antibody. Primary duck hepatocyte cultures generated from two-week-old DHBV-negative ducklings were treated with recombinant duIFN-λ3 or control-treated. Oligoadenylate synthetase-like (OASL), Mx-1 and IFI-35 mRNA expression were assessed by real-time PCR/RT-PCR.

RESULTS

The predicted 185 amino acid protein had an amino acid identity of 63% and 37% with chicken and human IFN-λ3 proteins, respectively. The duIFN-λ3 structure by homology modeling was similar to that of human IFN-λ3. Mapping the duIFN-λ3 cDNA with duck genomic sequences revealed a five exon-four intron gene structure similar to that of chicken and human IFN-λ3 genes. Recombinant duIFN-λ3 up-regulated OASL and Mx-1 mRNA expression by 6 hours.

CONCLUSIONS

Our observations suggest evolutionary conservation of genomic organization and structural features implicated in receptor binding of IFN-λ3 and demonstrated bioactivity of the expressed duIFN-λ3 protein. The identification and expression of duIFN-λ3 will allow the study of the role of type III interferon in the immunopathogenesis of DHBV infection and may facilitate the exploration of novel immunotherapeutic strategies in the duck hepatitis B infection model.

Supervisor: Dr. Klaus Gutfreund

Anti-TNF Dose Escalation in Inflammatory Bowel Disease

Christopher Ma, Darryl Fedorak, Karen I. Kroeker, Leo Dieleman, Richard N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Biologic agents targeting TNF-α (infliximab, adalimumab) are effective in maintaining remission in IBD patients but efficacy may wane over time. These secondary non-responders can regain clinical response from dose escalation. This study evaluates the proportion of IBD patients who require dose intensification, mean time to dose escalation, and risk factors predicting loss of response.

METHODS

This retrospective cohort study evaluated IBD patients who attained corticosteroid-free clinical response after induction and maintenance with infliximab or adalimumab from 2004-2012. Loss of response was defined by clinical indices, diagnostic imaging and inflammatory markers confirming disease activity. Dose escalation of infliximab (to 10mg/kg q8 weeks or 5mg/kg q4 weeks) or adalimumab (to 40mg weekly) and time to escalation were extracted by chart review. Subgroup analysis stratified patients by concomitant azathioprine use and site of infliximab infusion (community vs. university site). Kaplan-Meier analysis was used to assess maintenance of anti-TNF therapy over time.

RESULTS

500 IBD patients (82% Crohn's disease) who received infliximab (54%) or adalimumab (46%) were included. Mean follow-up was 23.0 and 19.8 months for infliximab and adalimumab, respectively. Among patients on infliximab, 43.7% (118/270) required dose escalation at a mean time of 19.6 months. 13.5% (31/230) of patients on adalimumab required escalation at a mean time of 18.6 months. Azathioprine was not associated with a statistically significant difference in time to dose escalation. Patients receiving infliximab at the University centre received dose escalation five months earlier than patients receiving treatment in community centres (17.5 vs. 22.9 months).

CONCLUSIONS

IBD patients failing biologic agents may have few therapeutic options. In this large cohort, one third of IBD patients required anti-TNF dose escalation, with higher rates among patients treated with infliximab compared to adalimumab. However, we found mean time to dose escalation (approximately 20 months) was significantly longer than previously reported in the literature.

Supervisor: Dr. Richard Fedorak

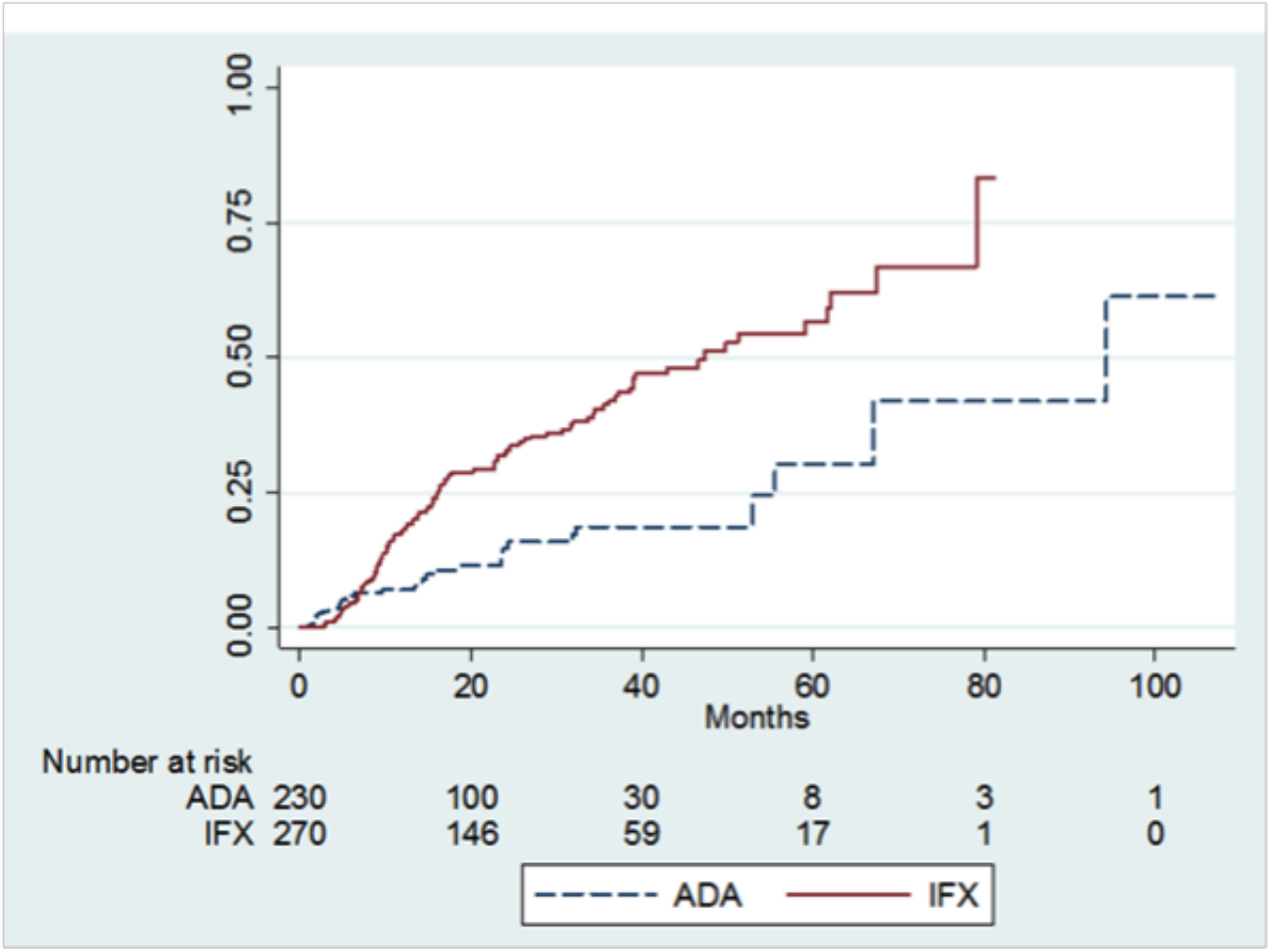


Figure 1: Kaplan-Meier curve for proportion of all IBD patients requiring dose escalation for infliximab and adalimumab

Varicella Zoster Meningitis Complications of Anti-TNF Therapy for Crohn's Disease: A Case Report and Literature Review

Christopher Ma, Brennan Walters, Richard N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Opportunistic viral infections are a well-recognized complication of anti-TNF therapy for IBD. Primary and latent reactivation varicella zoster virus (VZV) infections have been described in immunosuppressed Crohn's disease patients. However, central nervous system VZV infections are rare and there are no previous reports of VZV meningitis associated with anti-TNF therapy among IBD patients.

METHODS

We present the first reported case of varicella meningitis in a 40-year-old male with Crohn's disease treated with adalimumab and prednisone, and review the literature of VZV infections in immunosuppressed IBD patients.

RESULTS

Mr. MGA was a 40-year-old male who presented with a four-day history of increasing headaches, fevers, malaise, and reactivation dermatomal herpes zoster. There was no nuchal rigidity or focal neurological findings. His medical history included severe ileocecal Crohn's disease, for which he underwent an ileal resection and hemicolectomy. Infliximab was initiated after the disease recurred at the anastomosis in 2008 and although there was good response, an allergic reaction prompted a switch to adalimumab 40mg subcutaneously every other week. The patient was maintained on adalimumab and a tapering prednisone dose for six months prior to presentation.

Investigations revealed CSF lymphocytic pleocytosis (391x10^6 WBC, 98% lymphocytes), with positive CSF PCR for VZV. Empiric treatment with IV acyclovir (10mg/kg q8hrs) was initiated and adalimumab was discontinued. His neurological symptoms were not completely resolved, despite three weeks of acyclovir and three months of suppressive valacyclovir.

CONCLUSIONS

This is the first reported case of VZV meningitis occurring opportunistically in association with adalimumab and corticosteroid therapy in the IBD population, highlighting this population's risk of severe and atypical viral infections, and the need for early recognition and aggressive antiviral therapy. VZV vaccination should be considered prior to immunomodulation, but this may be difficult when anti-TNF agents are started as rescue therapy or patients have been on prolonged maintenance immunosuppression.

Supervisor: Dr. Richard Fedorak

Does vitamin D provide secondary prevention in cardiovascular disease? A systematic review

Zaina AlBalawi, Eloisa Colin-Ramirez, Justin Ezekowitz, Finlay McAlister
Supervisor: Dr. Finlay McAlister

INTRODUCTION

Our understanding of the vitamin D effect-spectrum has expanded since the novel discovery of vitamin D receptors (VDRs) in cardiac myocytes and smooth muscles. With cardiovascular disease (CVD) as the leading cause of morbidity and mortality worldwide, interest has focused on vitamin D as a simple and attractive therapeutic intervention for CVD prevention. Vitamin D deficiency has been linked to CVD in many epidemiological studies; however, causality has not been established yet.

A recent systematic review has addressed the role of vitamin D in primary prevention of CVD and has found no statistically significant effect with vitamin D supplementation although there is a large ongoing multi-center trial (The VITamin D and OmegA-3 TriaL, VITAL). There has also been a rising interest in the role of vitamin D in patients with established CVD. This systematic review aims to address whether vitamin D has a role in secondary prevention in patients with established CVD.

METHODS

Objectives

To evaluate the effect of vitamin D supplementation on secondary prevention of cardiovascular events, cardiovascular-related mortality, and all-cause mortality in patients with established CVD.

Search methods

The following databases were searched: MEDLINE, EMBASE, and CENTRAL with no language restrictions. We scanned bibliographies of relevant publications, and checked www.clinicaltrials.gov for ongoing trials.

Selection Criteria

We included RCTs that compared vitamin D, cholecalciferol (vitamin D3), or ergocalciferol (vitamin D2) to placebo in patients with CVD.

Data collection

Two authors independently screened for relevant titles, assessed for eligibility, and used a standard form for data extraction of included studies. A third author resolved any disagreement.

RESULTS

(In progress)

CONCLUSIONS

(In progress)

Complication rates of Jejunostomy Tubes in Comparison to Percutaneous Gastrostomy Tubes in a Regional Home Enteral Nutrition Support program

Ao, Peter; Sebastianski, Meghan; Selvarajah Vijeyakumar; Gramlich, Leah
Supervisor: Dr. Leah Gramlich

INTRODUCTION

The most common enteral access device for long-term enteral feeding is a percutaneous gastrostomy (PEG) tube which delivers nutrients directly into the stomach. However, patients with structural or functional abnormalities of the stomach require more distal tube placement into the jejunum. Jejunostomy tubes (J-tubes) are more technically challenging given the distal insertion site, and prone to complications due to smaller lumen diameters. There is a scarcity of literature comparing complication rates of J-tubes to the more common PEG tubes. The primary objective of this study is to compare tube re-intervention rates between J-tubes and PEG tubes.

METHODS

A retrospective chart review was performed on patients requiring enteral support followed by the Northern Alberta Home Enteral Nutrition Support Program (NAHENSP) from 2010-2011. This identified 64 J-tube patients and comparison was made to 65 randomly sampled PEG tube patients from the same year. Patients were followed for 3 years from tube insertion or until discharge from the NAHENSP, whichever was earliest. Comparisons were made between tube re-intervention rates, duration until tube re-intervention, and indications for re-intervention. Statistical analysis was performed using Cox Proportional Hazards regression.

RESULTS

Re-intervention rates for the J-tube group included 3.2 cases per 1000 patient days compared to 0.86 cases per 1000 patient days in the PEG group ($p<0.001$). The average duration to first tube re-intervention for J-tube and PEG tube patients was 160 ± 26 days and 331 ± 54 days, respectively ($p<0.01$). The most common causes of tube re-intervention in J-tube patients were dislodgement and obstruction at 36% and 22%, respectively. In PEG tube patients, the most common causes of tube re-intervention were routine and dislodgement at 55% and 27%, respectively.

CONCLUSIONS

J-tubes are associated with higher complication rates requiring tube re-intervention compared to PEG tubes. The main causes of J-tube re-intervention were dislodgement and obstruction.

Supervisor: Dr. Leah Gramlich

	J tube	G tube	P
N	64	65	
Demographics			
Mean age (years)	56.3 (SD=16.5)	58.9 (SD=13.8)	0.33
Male Sex	42 (65.6%)	50 (76.9%)	
Female Sex	22 (34.4%)	15 (23.1%)	
Previous GI Surgery	45 (70.3%)	7 (10.8%)	<0.001
Mean Tube size (mm diameter)	4.99 (SD=1.0)	6.72 (SD=0.2)	<0.001
Supplemental oral feeds	1.36(SD=0.5)	1.22 (SD=0.4)	0.071
Indication			
Esophageal/Gastric Cancer	29 (45.3%)	7 (10.8%)	<0.001
Head and Neck Cancer	9 (14.1%)	28 (43.1%)	<0.001
Stroke	1 (1.6%)	6 (9.2%)	0.055
Neurologic	7 (10.9%)	15 (23.1%)	0.067
Other	18 (28.1%)	9 (13.8%)	0.046
Results			
Person-time incidence rate (cases per 1,000 patient days)	3.2	0.86	<0.001
Days to first re-intervention	160 (SEM=26)	331 (SEM=54)	<0.01
Reason for Re-intervention			
Obstruction	20 (22.2%)	4 (12.1%)	
Dislodged	32 (35.6%)	9 (27.3%)	
Leakage	12 (13.3%)	2 (6.1%)	
Infection	9 (10.0%)	0	
Other	3 (3.3%)	0	
Routine	14 (15.6%)	18 (54.5%)	

Figure 1. Analysis of J-tube and PEG tube complcations

Obesity and chronic kidney disease: important determinants of periprocedural risk

Richa Chibbar, Anita Lloyd, Marcello Tonelli
Supervisor: Dr Marcello Tonelli

INTRODUCTION
The global epidemic of obesity is the key challenge facing health systems worldwide. Chronic kidney disease (CKD) is associated with excess cardiovascular risk and with periprocedural bleeding. Despite the technical challenges posed by these two common conditions, little is known about how they interact to affect periprocedural risk. We evaluated the risk of periprocedural complications in obese people with and without CKD.

METHODS
Alberta Health pays a supplemental fee to physicians when surgical or endoscopic procedures are performed on patients with documented BMI >35 kg/m2. We used these data to classify individuals undergoing a procedure as with or without class II obesity (>35 kg/m2) (based on the presence or absence of the supplement). CKD was defined by baseline eGFR<60 mL/min/1.73m2. We linked to the Alberta Health Vital Statistics file to ascertain mortality after 30d follow-up, and calculated adjusted odds ratios by obesity indicator and CKD status.

RESULTS
We studied 215,940 adults. Individuals with CKD were older, more often male, and had more comorbidity than those without. Individuals with obesity were slightly younger and more likely to be female, but had more comorbidity than those without. At 30 days after the procedure, unadjusted mortality was 0.05% (+obesity; -CKD), 0.09% (-obesity, -CKD), 0.6% (-obesity, +CKD) and 0.8% (+obesity, +CKD). After adjustment for age, sex and comorbidity, odds ratios for 30d mortality among these four groups were 0.58 (95%CI 0.28, 1.19), 1[ref], 2.43 (1.88, 3.13) and 4.08 (2.57, 6.47).

CONCLUSIONS
Among Alberta patients undergoing surgical and endoscopic procedures, those with obesity and CKD had the highest 30d mortality, while patients with obesity alone had the lowest. In fact, mortality was lower in this latter group than among those with neither obesity nor CKD, perhaps because of more vigilant patient selection. These findings highlight the complex relation between obesity, comorbidity, and clinical outcomes.

Supervisor: Dr Marcello Tonelli

Changes in Rate of Staphylococcus Aureus Bacteremia in Hemodialysis Population

Dr E Christie, Dr N Pannu, Dr L Saxinger
Supervisor: Dr Neesh Pannu

INTRODUCTION

Despite advances in antimicrobial therapies and preventative measures to decrease the rates of catheter-related bloodstream infection (CRBSI) in hemodialysis patients, these infections remain an overwhelming cause of morbidity and mortality. Serious complications from CRBSI occur in approximately 30% to 40% of patients. A landmark study published in 2003 demonstrated a significant mortality benefit of topical antibacterial ointment to central line sites in hemodialysis patients. This study triggered several protocol changes in the Northern Alberta Renal Program (NARP) units to decrease infection rates and improve patient outcomes. Our aim was to evaluate the effects of these protocol changes and to investigate any associated impact on the spectrum of pathogens causing CRBSI.

METHODS

All adult ESRD patients on hemodialysis via temporary or tunnelled catheters, with a documented bacteremia between January 1, 2003 - December 31, 2009 within the Infection Control Database were included. Our analysis included the overall CRBSI rate and the pathogens cultured.

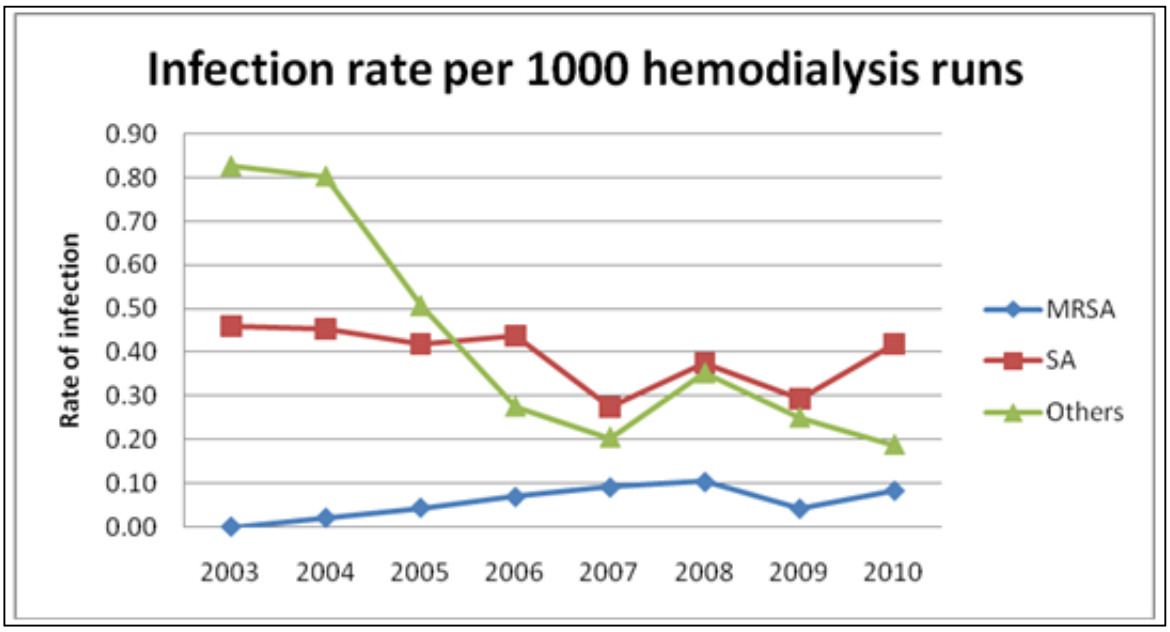
RESULTS

Our results demonstrated a decrease in the overall rate of infection over the study period, from 1.29 to an average of 0.69 bacteremias per 1000 HD runs, a 46.4% decrease. The analysis of the bacterial spectrum causing CRBSI revealed a decrease in the proportion of infections caused by common pathogens and a corresponding rise in the rate of Staphylococcus Aureus (SA). The percent of non SA bacteremias decreased from 95.2% to 39.4% from 2003 to 2010, where the rate of SA bacteremia increased from 4.8% to 60.6%.

CONCLUSIONS

This review suggests that NARP protocol changes in 2003 including the introduction of antibacterial ointment to catheter sites, has helped decrease the overall rate of CRBSI. However there has been a temporally associated increase in the proportion of more virulent pathogens, namely Staphylococcus Aureus. Further work is currently in progress to investigate the associated change in outcomes and infectious complications from CRBSI in the same population.

Supervisor: Dr Neesh Pannu


Infection rate per 1000 hemodialysis runs
Rate of infection
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
2003
2004
2005
2006
2007
2008
2009
2010
MRSA
SA
Others

Of Mice and Men: A case of Superwarfarin Intoxication

Cynthia Wu, Elena Liew, Subrata Datta, Liberty Liu
Supervisor: Cynthia Wu.

INTRODUCTION

Difethialone, a second-generation rodenticide (superwarfarin), is a potent long-acting anticoagulant. We present a case of difethialone intoxication resulting in a severe prolonged coagulopathy. We will outline the underlying pathophysiology, discuss important management points, and review previously reported superwarfarin poisoning cases.

METHODS

A 45-year-old female with history of anorexia nervosa, depression, and deliberate self-harm presented with epistaxis, menorrhagia, syncopal episodes, and a large right thigh hematoma that developed after a fall. By history, the patient was attempting to commit suicide and had been ingesting increasing amounts of rodenticide (active agent: difethialone 0.0025%) over the course of several months.

RESULTS

Initial investigations revealed significant anemia and markedly elevated INR and PTT, with normal liver enzymes, platelet count, and fibrinogen level. The anemia and coagulopathy were emergently corrected with PRBC transfusion, 3000 units of prothrombin complex concentrate (PCC), and Vitamin K 10mg IV. Vitamin K was not continued on the first day following admission and the INR, which had fully corrected after PCC administration, began to rise steadily to a peak of 1.6. Concurrently, the hemoglobin began to fall and the hematoma demonstrated clinical expansion. High-dose regular vitamin K was then restarted at 50mg PO QID and both laboratory and clinical parameters rapidly stabilized and improved thereafter. The patient was discharged home with ongoing vitamin K therapy and intensive follow up with psychiatry and hematology

CONCLUSIONS

Thigh hematoma can be an acute life-threatening presentation of superwarfarin poisoning. Warfarin-based medications act as vitamin K antagonists and induce coagulopathy by preventing gamma-carboxylation of vitamin K dependent factors, a chemical step required to produce fully active factors. Management of active bleeding should include factor replacement with frozen plasma or PCC, as well as concomitant immediate and extended duration treatment with high dose vitamin K to correct the coagulopathy until the drug is cleared from the system.

Supervisor: Dr. Cynthia Wu.

Cockroach allergen suppresses CCL26 expression and production in bronchial epithelial cells: a protective effect?

Cheryl Lane, Vivek Gandhi, Drew Nahirney, Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Allergic airway diseases affect a growing proportion of our population resulting in significant morbidity to patients and cost to the healthcare system. Further understanding of the molecular pathways underlying this disease will result in new therapeutic options. Proteinases associated with inhaled aeroallergens are a trigger for the inflammatory cascade. Cockroach allergens induce a potent inflammatory cascade in human airways that promotes Th2 immunity. Our aim is to determine if proteins in cockroach extracts can influence inflammatory cascade resolution in human airways, in addition to inducing allergic inflammation. Our original observation is that cockroach extract (CE) suppresses IL-13 mediated CCL26 release from airway epithelial cells. We hypothesize that CE suppresses IL-13 induced CCL26 production in human bronchial epithelial cells via a receptor-mediated mechanism.

METHODS

BEAS-2b and normal human bronchial/tracheal epithelial cells were stimulated with IL-13 or IL-4 in the presence or absence of CE. PAR-2 activating peptides were used in similar experiments to determine whether the CE effect was mediated through PAR-2 activation. Real-time PCR was utilized to quantify expression of CCL26 mRNA. Enzyme-linked immunosorbent assay quantified IL-13 degradation by CE and extracellular release of CCL26.

RESULTS

CE exerted a 70% inhibition (n=1) and a 99% inhibition (n=2), respectively, in CCL26 mRNA expression after twenty-four hours of IL-13 stimulation in primary and immortalized cell lines. Heat-inactivated CE had no impact on IL-13-induced CCL26 release. CE also inhibited the IL-4-mediated induction of CCL26. This effect is PAR-2 independent and not affected by COX inhibition. Preliminary results suggest IL-13 was not cleaved by CE during cell stimulation.

CONCLUSIONS

Heat labile CE proteinases inhibit Th2 cytokine induced CCL26 production from bronchial epithelial cells. Further work is necessary to determine the importance of serine protease activity to this mechanism and to explore whether this is a novel protective cellular mechanism activated during overwhelming inflammation.

Supervisor: Dr. Harissios Vliagoftis

Bone Density in Adults with Moderate-Severe Asthma in Western Canada

Pen Li1, Laith Ghazala1, Erin Wright2, Jeremy Beach1, Donald Morrish1, Dilini Vethanayagam
Supervisor: Dr. Dilini Vethanayagam

INTRODUCTION

Directed glucocorticoid (GC) therapy through inhalational drug delivery is recommended for management of patients with asthma, in conjunction with intranasal therapy for those with associated chronic rhinosinusitis. Occasionally, systemic glucocorticoid use is also required. In individuals with moderate-severe asthma in particular, cumulative steroid dose over time should be considered when titrating steroid therapies and evaluating for associated complications. The objective of this study was to evaluate the prevalence of osteopenia/osteoporosis as determined by bone densitometry in subjects referred and subsequently followed through the Edmonton Regional Severe Asthma Center.

METHODS

A retrospective chart review was carried out with recording of demographics, physiology and bone density assessments (dual-energy x-ray absorptiometry [DXA]). The overall steroid exposure of an individual was recorded, including type, duration, route, and cumulative dose. We then compared the frequency of osteopenia/osteoporosis in patients requiring continuous systemic GCs (Group 1), intermittent systemic GCs (Group 2), or those only on local inhaled +/- intranasal GCs (Group 3).

RESULTS

A total of 32 charts were reviewed. The average accumulated steroid dose for Group 1 was 9.89mg daily prednisone equivalent. The frequency of osteopenia/ osteoporosis was higher in group 1 (73%), than group 2 (46%). For group 3, two individuals had DXA performed at the time of chart review, and these were both normal. The majority (26/32) of subjects were on treatment for concomitant rhinosinusitis. Of note, 6 (%) patients in Group 1 were on treatment with bisphosphonates., X (%) in group 2, and Y (%) in group 3.

CONCLUSIONS

The frequency of osteopenia/osteoporosis in steroid-dependent asthma patients may be underestimated by treatment with bisphosphonate therapy. Earlier screening for osteoporosis should be done for asthma patients on both continuous and intermittent systemic steroids. The adverse effects of steroids on bone mineral density is a cumulative process that should be considered when initiating steroid treatment, even in pediatric or young adult asthma patients.

Supervisor: Dr. Dilini Vethanayagam

Retrospective analysis of dose intensity, toxicity, and clinical outcomes in 5-fluorouracil based regimens in the adjuvant treatment of colorectal cancer

Jonathan Loree, Karen Mulder, Sunita Ghosh, and Jennifer Spratlin
Supervisor: Dr. Jennifer Spratlin

INTRODUCTION

Adjuvant colon cancer treatment relies on 5FU containing regimens as either an IV formulation or as the oral pro-drug, capecitabine, combined with oxaliplatin (FOLFOX6 and CAPOX). We performed a retrospective chart review comparing average relative dose intensity (ARDI), overall survival (OS), disease free survival (DFS), and toxicity profiles of these two regimens.

METHODS

233 patients between January 1, 2006 and December 31, 2011 received chemotherapy combining either FOLFOX6 (n= 128) or CAPOX (n=105). ARDI was compared by calculating a percent of target dose achieved in the average cycle for each patient. Data on OS, DFS, baseline demographics, and toxicities were gathered. Follow up was complete until November 1, 2012.

RESULTS

Oxaliplatin ARDI was significantly lower in those treated with CAPOX compared to FOLFOX6 (80.72% vs 87.11%, p=0.0033), as was the 5-FU component (87.10% vs 93.60%, p<0.0001). More patients treated with CAPOX had dose limiting toxicities (84.76% vs 73.40%, p=0.039), and there were significantly more Grade 2 and higher toxicities in those on CAPOX (p<0.0001). A similar percentage of goal number of cycles was achieved between CAPOX and FOLFOX6 (87.38% vs 91.80%, p=0.13) and similar neuropathy was noted between groups. Survival analysis demonstrated similar OS and trends towards improved DFS with CAPOX (1 year – 89.55% vs 83.20%, 3 year – 67.13% vs 58.01%, p=0.051). Stage specific analysis showed stage III patients had improved DFS with CAPOX (1 year – 93.36% vs 86.69%, 3 year- 71.58% vs 68.10%, p=0.042) and trends towards improved OS with CAPOX (1 year – 100% vs 95.56%, 3 year – 95.08% vs 80.17%, p=0.16). The groups had similar age, gender, tumor size, and node status, while ECOG was slightly higher with FOLFOX6 (0.589 vs 0.419, p=0.0315).

CONCLUSIONS

While patients on CAPOX had significantly lower doses of oxaliplatin and the 5-FU component of their treatment they appear to have improved outcomes compared to FOLFOX6.

Supervisor: Dr. Jennifer Spratlin

Volume overload in Remote-dwelling Hemodialysis Patients: an Opportunity to Improve Care.

Marcello Tonelli, Anita LLoyd, Brian Nadler
Supervisor: Dr. Marcello Tonelli

INTRODUCTION

Routine assessment and control of ECF volume is a key part of managing chronic hemodialysis patients. Hemodialysis patients who live further away from their nephrologists (“remote-dwellers”) usually dialyze in satellite facilities, and are clinically assessed less frequently than those treated in-centre. We hypothesized that ECF volume overload might be a reversible cause of morbidity and mortality in this patient population.

METHODS

Bioelectrical impedance analysis (BIA) can be performed at the bedside, and uses electrical ionic conduction to estimate total body water. BIA can be used to measure phase angle, which is a single parameter that inversely correlates with ECF volume. Shorter vector lengths (especially those <250 ohm/m) are independently associated with mortality in hemodialysis patients. We used the Hydra device to assess pre-dialysis vector length in a convenience sample of 81 remote-dwelling patients. Results were compared to 13 non-remote patients. We also examined the association between vector length and established markers of hypertension.

RESULTS

Mean age was 60 16 years, 51% were male, 54% had diabetes, and the mean number of comorbidities was 0.8 1.2. There were no significant differences in these characteristics between remote- and non-remote dwellers. Mean pre-dialysis and post-dialysis blood pressures in remote-dwellers were 136/68 and 128/67 respectively; mean vector length was 305 76 ohm/m. Corresponding values in non-remote-dwellers were 133/69, 136/65 and 327 59 ohm/m. There were no significant differences in mean systolic or diastolic blood pressures between remote- and non-remote-dwellers (both $p>0.1$). However, 21 (26%) of remote-dwellers had vector length <250 ohm/m, as compared to only 1(8%) of non-remote-dwellers ($p=0.15$). Shorter vector length was positively correlated with higher pre-dialysis systolic ($r=0.25$, $p=0.02$) and diastolic ($r=0.29$, $p=0.007$) blood pressure.

CONCLUSIONS

Correcting poor control of ECF volume overload in remote-dwelling hemodialysis patients may be a potential method for improving care in this population.

Supervisor: Dr. Marcello Tonelli

Towards Better Management Strategies:Analysis of Invasive Fungal Infection Risks in a Cohort of Severely Neutropenic Inpatients

Dr. Aliyah Pabani, Louise McBeath RN, Dr. Lynora Saxinger
Supervisor: Dr.Lynora Saxinger

INTRODUCTION

Invasive Fungal Infections (IFI) cause significant morbidity and mortality in neutropenic patients. Optimal management is controversial:risk based prophylaxis or preemptive therapy, and local epidemiology of IFI is pertinent in this decision. In 2009 UAH Infection Control began prospective IFI surveillance (IFI rate per 1000 neutropenic patient days). In this analysis, IFI incidence was examined by patient diagnoses and duration of neutropenia, to establish baseline local epidemiology prior to a change in management strategies.

METHODS

All neutropenic inpatients on 5F4 were identified an those who were neutropenic for > 10 days were followed for development of Probable or Definite IFI, defined by the 2008 EORTC Criteria. These cases were reviewed to determine the hematologic diagnosis, type of chemotherapeutic regimen, and total (not just hospitalized) continuous duration of neutropenia.

RESULTS

There were 139 neutropenic episodes (mean duration 29.4 d)in 100 patients, with 94 "severe" episodes in 71 pts (mean 40.9 d), 10 (14%) of whom had IFI with 5 deaths. The diagnosis, number patients, range of neutropenic days, and IFI incidence were as follows: AML induction/salvage, 50pts, 10-31d, 7 cases; AML consolidation, 11pts, 10-31d, 1 case; MDS, 13pts, 10-420, 0 cases; ALL, 3pts, 14-16d, 0 cases, OTHER, 39pts, 10-870d, 2 cases. Eight invasive candidiasis and 2 pulmonary aspergillosis cases were noted at a mean of 44d of neutropenia (range 0-76 days).

CONCLUSIONS

The IFI rate (predominantly candidiasis) in this severely neutropenic population is in the range of published studies, with significant related mortality. The range of neutropenic days observed in the diagnostic categories was broader than expected, with the highest IFI rate in AML induction-salvage, although the myeleodysplasia group had longer durations of neutropenia. Thus the type of therapy/underlying disease contribute to the risk of IFI independent of neutropenic duration, and this should inform IFI management strategies.

Supervisor: Dr.Lynora Saxinger

Bone Formation in the Lung: A Rare Case of Pulmonary Ossification

Noreen Rajwani
Supervisor: Dr. Meena Kalluri

INTRODUCTION

A 51 year old male with a complex medical history including Crohn's disease on methotrexate, unprovoked bilateral pulmonary emboli and Nocardia pneumonia presented with a two week history of increasing dyspnea on exertion. A CT chest revealed chronic reticulonodular interstitial pattern and PFT revealed a restrictive lung pattern with a severely reduced diffusion capacity. Lung biopsy revealed diffuse dystrophic ossification.

Pulmonary Ossification (PO) is a very rare disorder in which heterotrophic bone formation is present in lung tissue. The disorder can be idiopathic or secondary to an underlying chronic disorder. It is often under-recognized and diagnosed on autopsy.

Considering our patient’s afore mentioned extensive medical history, the purpose of our literature review is to determine:
1) What chronic diseases can cause PO?
2) What is the pathogenesis of PO?

METHODS

We conducted a literature search using Medline and Pubmed with a variety of MeSH terms such as “Pulmonary ossification, pathogenesis and causes.” This search yielded 20 results and after applying exclusion criteria only 17 were found to be relevant. Of these, two were reviews, two were retrospective analysis and thirteen were found to be case reports.

RESULTS

Development of PO occurs in areas of previous lung injury and requires an alkaline environment, cessation of pulmonary blood flow, presence of collagen and profibrogenic cytokines, extravasation, and metallic deposition. Non- idiopathic causes of PO include pulmonary diseases such as amyloidosis, metastases, pulmonary fibrosis, pulmonary venous hypertension and cardiac causes such as mitral stenosis and left ventricular failure.

CONCLUSIONS

The previous lung injury in our patient likely set up a milieu conducive to bone mineralization and formation of PO. The early recognition of PO is important as chronic diseases are becoming more prevalent in our aging population and early diagnosis will aid in appropriate treatment of this rare disease.

Supervisor: Dr. Meena Kalluri

Standardized Admission Order Sets for Acute Exacerbation of COPD: A breath of fresh air?

Noreen Rajwani
Supervisor: Dr. Mohit Bhutani

INTRODUCTION

Patients with Chronic Obstructive Pulmonary Disease (COPD), a respiratory disorder characterized by progressive airflow limitation, are prone to exacerbations of COPD (AECOPD) leading to hospitalization.

Several principles of care in the management of AECOPD including medication, oxygen testing, referral to rehabilitation and allied health care utilization were shown to vary between differing admitting services. In an attempt to improve care, standardized admission orders for AECOPD, based on current Canadian guidelines for the management of AECOPD, were developed and made available for use within the University of Alberta hospital.

METHODS

This study is a retrospective review of admissions to UAH for AECOPD in patients where the standardized admission orders were used. We will review 100 consecutive admissions for AECOPD in which the standardized admission orders were used. All admissions beginning from September 1, 2012 will be reviewed. Data collected will be compared to existing information from a prior audit. This will include comparing inpatient medical management and utilization of allied health services.

RESULTS

Data collection is currently in progress, however we hypothesize the admission order set will standardize practice and as a result, patients will be treated with currently accepted guideline care. As such, there will be less variance in the treatment of patients presenting with an AECOPD.

CONCLUSIONS

This study has implications not only in standardizing care among differing admitting services but also in improving compliance in treating AECOPD as per current guidelines. We hope to demonstrate overall reduced lengths of stay in hospital and a decrease in health care associated costs.

Supervisor: Dr. Mohit Bhutani

The Milky (Path)Way of Proteinosis: An Experimental Therapy for Pulmonary Alveolar Proteinosis

Noreen Rajwani
Supervisor: Dr. Cynthia Wu

INTRODUCTION

A 35-year-old male presented with a six-week history of exertional dyspnea and a non-productive cough. He was hypoxemic and a CT chest showed bilateral diffuse interstitial and airspace opacities. Bronchoscopy yielded bilateral milky white secretions and biopsy findings were consistent with Pulmonary Alveolar Proteinosis (PAP). The patient received whole lung lavages, the current standard of care, but continued to decline.

Primary Pulmonary Alveolar Proteinosis is a rare but often fatal disorder in which surfactant related lipoprotein accumulates within alveoli leading to impairment of gas exchange and respiratory failure. Antibodies against Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) have been found in Acquired PAP.
GM-CSF is thought to play a protective role in in the lung and therefore this study examined two questions:
1)Is GM-CSF effective in the treatment of PAP?
2)If so, what is the proposed mechanism of action of exogenous GM-CSF?

METHODS

We conducted a literature search using Medline and Pubmed with a variety of MeSH terms such as “Pulmonary Alveolar Proteinosis and Drug Therapy.” This search yielded 80 results. After applying exclusion criteria, only 26 were relevant. These included one meta-analysis, seven clinical trials, three systematic reviews, two retrospective analyses, one prospective study, eight case reports and four basic research studies.

RESULTS

GM-CSF can be effective in treating PAP as evidenced by improvement in symptomatology, PFTs and imaging in responders. It does so via differentiation of macrophages that then increase surfactant clearance and improve oxygen transfer.

CONCLUSIONS

The use of GM-CSF has proven to be efficacious in patients with Acquired PAP. In addition, it may be an appropriate and less morbid therapeutic alternative to whole lung lavage and subsequent lung transplant in non-responders.
Our patient received GM-CSF therapy for approximately one year with a vast improvement in his symptomatology and complete resolution of abnormalites on his chest CT, ABGs and PFTs.

Supervisor: Dr. Cynthia Wu

On the Precipice: An analysis of medical students' narrative reflections as they look toward transitioning to the clinical years

Jason Soo, Pamela Brett-MacLean, Marie-Therese Cave, Anna Oswald
Supervisor: Dr. Anna Oswald

INTRODUCTION

Many undergraduate medical education programs include preclinical, basic sciences and clinical studies components.The transition from preclinical to clinical training is often characterized as stressful and challenging for medical students (1-3). A number of studies have found that preclinical students report both excitement and anxiety about their role and responsibilities in the clinical setting (4). Despite changes to the medical curriculum that have introduced more case-based learning, medical students have shared that they feel challenged imagining how they will apply their theoretical learning to future clinical contexts (5). In this poster, we outline second year medical students' perceptions and reflections regarding their first two years in medical school, and have included some of the experiences that stood out in their preclinical education.

METHODS

Thirty five second-year medical students in the Faculty of Medicine and Dentistry at the University of Alberta Medical School participated in a narrative reflective practice session that was included at the end of their longitudinal, Patient-Centred Care course. They were asked to write a short ½ page personal reflection on their learning journey as they looked toward entering clinical years of their training. We performed a qualitative narrative analysis on these written reflections for emerging themes.

RESULTS

35 narrative reflective writing assignments were analyzed. The major themes extracted included: 1. Evaluative reflections regarding what students found useful or not useful in their preclinical education, 2. Student's feelings of various degrees of preparedness for clerkship and medicine in a professional sense, 3. Expectations relating to identity (who they are becoming personally and professionally), and the practical side of being a doctor.

CONCLUSIONS

Students' reflections on their experiences through the transitional period between preclinical years and clerkship can help us better understand the problems that students face and potentially inform curriculum changes.

Supervisor: Dr. Anna Oswald

Do patients with bronchiectasis benefit from Pulmonary Rehabilitation?

A. Whidden, E.Wong, M.Bhutani, M.K. Stickland
Supervisor: Dr. Ashley Whidden

INTRODUCTION

Bronchiectasis is defined as dilatation and destruction of bronchi generally caused by infection and inflammation, and leads recurrent exacerbations, dyspnea, and fatigue with decreased exercise tolerance and activity levels. Pulmonary rehabilitation (PR) has been recommended as the standard care for patients with chronic obstructive pulmonary disease (COPD), but data is limited regarding the effects of PR on patients with bronchiectasis. PURPOSE: To evaluate health outcomes from PR in bronchiectasis.

METHODS

A retrospective review was conducted on 49 patients with bronchiectasis enrolled in a 6-8 week PR program and results were compared to 133 COPD patients enrolled in PR over the same period. Six-minute walk distance (6MWD) and quality of life (measured by St. Georges Respiratory Questionnaire (SGRQ)) were evaluated before and after PR.

RESULTS

At baseline, the two groups were similar in terms of age (67 ± 14yr, 67 ± 11yr), BMI (27 ± 7 kg/m2, 29 ± 7 kg/m2), attendance to PR (12 ± 4 sessions, 12 ± 5 sessions), baseline exercise capacity and quality of life scores. Bronchiectasis patients had less smoking history (25 ± 13pk yr vs. 43 ± 21pk yr), and better lung function (FEV1 = 61 ± 19% vs. 52 ± 22%) compared to COPD. With PR, bronchiectasis patients significantly increased 6MWD from 462 ± 30m to 514 ± 28m with PR, similar to the response observed in COPD patients (433 ± 18m to 452 ± 17m). A significant improvement in SGRQ scores with PR was observed in bronchiectasis patients (from 42 ± 3% to 37 ± 3%), which was also similar to the improvement in the COPD group (48 ± 2% to 43 ± 2%).

CONCLUSIONS

These results demonstrate that patients with bronchiectasis benefit from pulmonary rehabilitation and support their inclusion in PR programs.

Supervisor: Dr. Ashley Whidden

Prevalence Of Herpes Zoster Infection In Patients With IBD Increases With Increasing Immunosuppression Therapy

C. Lu, K. Manhas, S. Bakkari, L. Dieleman, V. Huang, K.I. Kroeker, A. Syed, R.N. Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Anti-TNFα (tumor necrosis factor) and immunosuppressive (azathioprine, 6-mercaptopurine, or methotrexate) agents represent important advancements in the treatment of inflammatory bowel disease (IBD). However, these medications have been associated with opportunistic infections including severe and occasionally fatal cases of herpes zoster infection. To date no study has examined the frequency of herpes zoster infections (shingles) in this at risk IBD population.

METHODS

We conducted a prospective cross-section study involving consecutive patients with IBD attending the IBD outpatient clinic at the University of Alberta between July 2011 and October 2012. 201 eligible patients who were willing to participate completed an eight-item questionnaire to determine clinical occurrences of previous herpes zoster infection and to define the infection with respect to time of IBD diagnosis and treatment. Risk difference analyses were performed on the following groups of patients: (1) controls (no anti-TNFα or immunosuppressive therapy), (n=33); (2) patients only on immunosuppressive therapy (n=16); (3) patients only on anti-TNFα therapy (n=61); (4) patients on both anti-TNFα agent and immunosuppressive therapy (n=91).

RESULTS

The mean age and gender in each group was similar and not statistically different. The number of patients on corticosteroids and disease flares was evenly distributed between each group. The prevalence of herpes zoster infection in group 1 (controls) was 3.0% (1/33), group 2 (immunosuppressive only) was 6.3% (1/16), group 3 (anti-TNFα therapy only) was 11.5% (7/61), and group 4 (both anti-TNFα agent and immunosuppressive therapy) was 13.2% (12/91). The risk of shingles was 8.9% (CI 1.25% to 16.5%) higher in patients taking any immunosuppressive medication when compared to controls.

CONCLUSIONS

This is the first study to report the prevalence of herpes zoster infection in patients with IBD on varying immunosuppressive therapies. Patients with IBD have a prevalence of herpes zoster infection that is higher than the normal population. This prevalence increases with increasing immunosuppressive and biologic therapy.

Supervisor: Dr. Richard Fedorak

Development of a New Equation to Estimate GFR in Cancer Patients

MP Chu, L McCaw, C Stretch, J Hanson, M Kuzma, V Damaraju, VB Baracos, MB Sawyer
Supervisor: Dr. Michael B. Sawyer

INTRODUCTION

Renal function affects chemotherapy pharmacokinetics. Carboplatin dosing by Calvert's formula is more pharmacologically rational, but requires an accurate glomerular filtration rate (GFR).Calvert argues that this requires measuring GFR (mGFR) instead of an estimated GFR (eGFR).Considering skeletal muscle is the major source for creatinine, this study looks to develop a new eGFR equation in cancer patients using lean body mass (LBM).

METHODS

We prospectively followed 22 stage IV cancer patients (10 female, 12 male; median age 69) who received carboplatin. mGFR by 24 hr creatinine clearance was compared to eGFR by Wright, Cockcroft-Gault (CG), CKD-EPI, MDRD and CT-determined LBM (eGFR = [Muscle Surface Area X 42]/CR). Simulated carboplatin dosing with each eGFR was then compared retrospectively in 100 Non-Small Cell Lung Cancer (NSCLC) patients for accuracy.

RESULTS

MDRD, CG, and Wright equations correlated variably with mGFR (R2 0.47, 0.57, and 0.69 respectively). Conversely, mGFR strongly correlated with LBM eGFR (R2 0.84). Table 1 compares eGFR calculations with mean residual error. In simulated carboplatin dosing of 100 Stage IV NSCLC patients using LBM and CG eGFR, the mean residual error of the CG-determined carboplatin dose was 10% (0.5% min, max 39.7%, median 9.3%), assuming the LBM eGFR was better at estimating eGFR. This means that in approximately half of patients, carboplatin dose may be incorrect by CG if the new LBM eGFR method is truly more accurate.

CONCLUSIONS

We propose a new formula for eGFR in cancer patients that appears superior to current formulas and may have implications for chemotherapy efficacy and toxicity. Studies to validate this formula are under way.

Supervisor: Dr. Michael B. Sawyer

Equation to Predict GFR	Mean	Median	Min	Max
LBM	9.0	5	1	23
Wright	11.5	10	0	30
CG	22.6	15	1	60
CKD-EPI	18.2	17	1	47
MDRD	19.8	19	2	53

Table 1: eGFR Calculations and Mean Error from Measured Values

Efficacy and safety of single agent (SA) or combination (CO) adjuvant chemotherapy (AC) in elderly patients with colon cancer: A Canadian cancer institute experience

Christina Kim, Jennifer L. Spratlin, Sunita Ghosh, Dawn Elizabeth Armstrong, Karen E. Mulder
Supervisor: Dr. Jennifer Spratlin

INTRODUCTION

The pattern of AC use, the toxicity profile, & survival benefit in elderly patients (pts) with colon cancer (CC) is unclear. We sought to: 1) determine whether pts ≥65 yo with stage III CC were being offered SA or CO AC; 2) evaluate the reason for selecting SA vs. CO AC; 3) evaluate the toxicity profile of SA & CO in the elderly; and 4) determine whether a survival benefit exists for elderly pts receiving CO AC.

METHODS

Pts ≥65 diagnosed with stage III CC at the Cross Cancer Institute from 2004-2010 were identified from the provincial cancer registry. A retrospective analysis of electronic & paper patient records was performed to identify baseline characteristics, AC protocols used, toxicity, dose reductions, dose delays and survival.

RESULTS

258 pts ≥65 years old were diagnosed & treated with AC from 2004-2010. 168 were treated with SA & 90 with CO AC. The most common reasons for choosing SA AC were patient preference (64%), comorbidities (17%), & lack of drug coverage by provincial formulary (16%). 93 pts ≥age 75 were treated with SA AC, whereas only 20 pts ≥75 were treated with CO AC. Grade 3 & 4 non-hematologic toxicity was more common with CO AC (43% vs. 27%). 67%, 71% & 29% received dose delays, reductions or drug discontinuation in the SA group, respectively. 72%, 58% & 34% received dose delays, reductions or drug discontinuation in the CO group respectively. The 5 year OS was 73% in pts who received SA AC, compared to 84% in those who received CO AC.

CONCLUSIONS

In elderly pts treated with AC for stage III CC, SA AC is used more frequently than CO AC, based on age, comorbidities, & patient choice. Toxicity with CO AC in elderly pts is high, but may carry a potential survival benefit for those who receive it.

Supervisor: Dr. Jennifer Spratlin

LARGE COLORECTAL POLYP REMOVAL BY ENDOSCOPIC MUCOSAL RESECTION: AN OUTCOME ANALYSIS

Ali Kohansal, Samson Haimanot, Clarence Wong, Christopher Teshima, Sergio Zepeda-Gomez, Richard Sultanian, Gurpal S. Sandha
Supervisor: Dr. Gurpal Sandha

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer related mortality. The majority of CRC's arise from adenomatous polyps. A majority of large sessile polyps (LSPs) can be excised using endoscopic mucosal resection (EMR). Concerns remain regarding complete excision at site of polypectomy. There is no published Canadian literature regarding outcomes following EMR of LSPs.

METHODS

We reviewed endoscopy records of LSPs resected from 2009-2012. LSPs were defined as those measuring 2 cm or more in greatest diameter, based on endoscopy or histology reports. Patient demographics, indications and details of the EMR, histopathology of LSPs, complications, and follow up colonoscopy were reviewed.

RESULTS

46 patients (mean age 67 yrs, range 33-86, 29 male) underwent EMR of LSPs. Average size was 3.2 cm (range 2-6) and 24/46 (52%) located in the left colon. Complete EMR was achieved in 44/46 cases (96%); surgery was required for 2 cases. Piecemeal EMR was required for removal in 37/46 LSPs (80%) . Histology was available for 44/46 (96%) with presence of high grade dysplasia (HGD) in 17/44 cases (39%). LSP size >3 cm was associated with higher incidence of HGD on histology (OR 4.73 CI =1.2153 to 18.3889, p=0.0213). Average time to follow up colonoscopy was 276 days (range 98-731); 31/46 patients (67%) underwent follow up colonoscopy within 12 months. Recurrence at the site of EMR occurred in 6/31 (19%) cases. Those with prior biopsies, or partial removal had a higher rate of recurrence (6/19 vs. 0/12, p=0.0252). There was no significant correlation between polyp size and recurrence. Significant complications occurred in 2/46 patients (4%; 2 perforations). There were no incidents of significant post-polypectomy bleeding.

CONCLUSIONS

EMR for LSPs is an effective and safe procedure.Biopsy or removal appear to contribute towards recurrence. These findings warrant studies with larger sample size and longer follow up to help identify factors contributing to polyp recurrence.

Supervisor: Dr. Gurpal Sandha

CLINICAL OUTCOMES OF PALLIATIVE STENTING FOR MALIGNANT BILIARY OBSTRUCTION

Ali Kohansal, Samson Haimanot, Robert Bailey, Christopher Teshima, Sergio Zepeda-Gomez, Richard Sultanian, Gurpal Sandha.
Supervisor: Dr. Gurpal Sandha

INTRODUCTION

Malignant biliary obstruction leads to jaundice which may cause related sequalae of pruritis, pain, and anorexia. Palliative decompression aims to improve patient quality of life (QOL). Stenting via ERCP is relatively less invasive yet effective for symptoms such as pruritus. However, it is unclear whether decompression in the absence of symptoms attributable to biliary obstruction is equally effective in improving QOL associated with hyperbilirubinemia.

METHODS

We reviewed all ERCPs undertaken for palliative biliary stent insertion from 2009-2011. Patient demographics, indication for procedure, type of stent (plastic vs. metal), complications and need for follow up ERCP were reviewed.

RESULTS

From 2009-2011, 1306 ERCPs were performed. 48 patients underwent 80 ERCPs for palliative stenting of malignant biliary stricture. Pancreatic cancer was the most common cause, accounting for 32/48 (67%). Jaundice was present in 44/48, and the sole presenting symptom in 17 patients. The average bilirubin level was 210 umol/L at the time of ERCP. Metal biliary stents were placed in 31/48 (65%) and plastic biliary stents in 17/48 (35%) of patients. Patients with metal stents underwent a total of 40 ERCPs (mean 1.3 ERCP/pt) vs. 40 ERCPs in those with plastic stents (mean 2.4 ERCP/pt). Complications occured in 2/40 (5%) ERCPs for metal vs 2/40 (5%) for plastic stents. Average survival time following metal stent insertion was 161 days (range 5-537) vs. 128 days for plastic stent (range 14-379). The average hospital stay after metal stents was 24 vs. 40 days for plastic stents ($p=0.1$)

CONCLUSIONS

Initial metal stent placement for palliation of malignant biliary obstruction results in fewer ERCPs and a shorter hospital stay, contributing to reduced overall health care costs and improvement in QOL. However to assess whether biliary decompresson for asymptomatic hyperbilirubinemia leads to overall improvement of QOL, prospective studies comparing biliary stenting and observation without stenting are needed.

Supervisor: Dr. Gurpal Sandha

Evaluation of a secure, store-and-forward teledermatology system to facilitate Emergency Physician consultations

A Kurian and J Rao
Supervisor: Dr. Jaggi Rao

INTRODUCTION

We describe an ongoing Store-and-forward teledermatology (SFT) pilot project in Edmonton, Alberta. The objectives of this study were to: 1. To determine emergency physician (EP) satisfaction with SFT. 2. To document patient satisfaction with the project. 3. To evaluate the efficiency and practicality of remote dermatology consultation.

METHODS

Patients with skin-related complaints were invited to participate. Patients were selected at the discretion of the attending EP. Digital photographs of the patient's skin lesions, and the ED chart were obtained. All images were uploaded to a secure and confidential web-based teledermatology platform. After remote review, the teledermatologist provided 1) a diagnostic impression, 2) an educational note, and 3) management suggestions. All patients were invited for follow-up. Participating Emergency Physicians, as well as all patients who attended dermatology follow-up were invited to complete a survey documenting their satisfaction and experience with the process

RESULTS

A total of 480 patients participated in the first 12 months of this project ranging from newborn to 97 years of age. Average time from consult request to completion was 16 minutes (range 1 to 47 minutes). 96% of patients received prescription recommendations, 22% received surgical recommendations, and 5% received reassurance with the option for dermatology follow-up only. 67% of Emergency Physicians responded to the survey, and all reported overall satisfaction with the process. Of the 480 participating patients, 52 were subsequently seen in clinic for dermatology follow-up. 90% completed surveys at the time of follow-up, and all reported overall satisfaction with the teledermatology process.

CONCLUSIONS

SF Teledermatology can improve patient care, expedite the consultation process, offer timely access to specialist care, and contribute to continuing medical education. It may also represent a cost-saving opportunity, by avoiding unnecessary repeat visits.

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