10th ANNUAL

ARC

RESEARCH

D AY

Wednesday, November 14, 2018
11:00 am – 5:00 pm
Lower Foyer, Bernard Snell
8440 – 112 Street
University of Alberta
Edmonton, AB
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Message from the ARC Research Director

Dear Colleagues,

I would like to extend a warm welcome to our 10th Annual ARC Research Day to all of you in celebrating important contributions made by our trainees during the past year. During this ARC Research Day, we highlight the commitment of our Centre to excellence in research, education, and clinical care. This year we have 29 abstract submissions for poster presentations. This is evidence of our collaboration across disciplines that will continue to foster new research efforts and garner support from many funding sources.

The mission of ARC Research Day is to promote research, provide opportunities for collaboration and mentorship, and facilitate collegial activities between researchers and clinicians involved in respiratory medicine. It also gives an opportunity to many of our younger trainees to present their work for the first time to an audience outside of their own laboratory. These interactions will give them the experience and confidence to present to wider audiences in national and international meetings, as well as giving them an opportunity to win presentation awards. I would like to encourage everyone to come to the poster session in the afternoon and interact with the trainees. You will immediately notice how enthusiastic they are in presenting their work and getting feedback from all attendees.

I would like to extend my special thanks to our administrative assistants, Cassie Tobin, Giselle Procter, Iris de Guzman, and Darcy Wolfspirit who have provided superb support through the process of organizing the ARC Research Day and have done an excellent job of organizing this important event.

The 21st Annual Brian J. Sproule Lectureship in Pulmonary Medicine will be held in conjunction with ARC Research Day, presented by Alberta Respiratory Centre (ARC). We will be commemorating Dr. Sproule, who is greatly missed, and will honour his memory in years to come. We are delighted to have Dr. Denis E. O’Donnell from Queen’s University as this year’s distinguished Brian J. Sproule lecturer. Dr. O’Donnell’s lecture will follow poster award presentations in Classroom F, from 4:00 p.m. to 5:00 p.m.

Dr. O’Donnell has been supported by a Dean’s Lecture Series Award for Visiting Speaker. I would also like to thank our sponsors Novartis, AstraZeneca, GSK, and Grifols for providing their valuable support to make this a successful event. I hope to see you all during the poster session and the Brian J. Sproule Lectureship.

Paige Lacy, PhD
Research Director, Alberta Respiratory Centre
Professor, Department of Medicine
University of Alberta
## Program

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Adjudication Committee

We would like to thank the members of the Adjudication Committee who have generously donated their time and efforts to adjudicate the poster presentations of Pulmonary Residents, Core Internal Residents, Graduate Students, and Undergraduates.

Dr. Alim Hirji, Assistant Professor, Pulmonary Medicine

Dr. David Marchant, Assistant Professor, Medical Microbiology & Immunology

Dr. Dean Befus, Professor Emeritus, Pulmonary Medicine

Dr. Ron Damant, Interim Division Director, Pulmonary Medicine

Dr. Francis Davoine, Associate Professor, Campus Saint-Jean

Dr. Kieran Halloran, Assistant Professor, Pulmonary Medicine

Dr. Anne Hicks, Assistant Professor, Pediatrics

Dr. Meena Kalluri, Associate Professor, Pulmonary Medicine

Dr. Anita Kozyrskyj, Professor, Pediatrics

Dr. Richard Long, Professor, Pulmonary Medicine

Dr. Michael Stickland, Professor, Pulmonary Medicine

Dr. Alvaro Osornio Vargas, Professor, Pediatrics

Dr. Harissios Vliagoftis, Professor, Pulmonary Medicine
DEAN’S LECTURE SERIES
& Brian J. Sproule Lectureship

The Pathophysiology of Dyspnea in Chronic Lung Diseases

Wednesday, November 14, 2018
4 - 5 p.m.
2J4.02 (Classroom F) WMC
W C Mackenzie Health Sciences Centre

Refreshments will be made available

The Lectureship will follow the Annual ARC Research Day Award Presentations

featuring
Dr. Denis E. O’Donnell
Professor of Medicine, Queen’s University, Kingston, Ontario
Senior Clinician Scientist and Director, Respiratory Investigation Unit, Kingston Health Science Centre
Recognized internationally for his work with several prestigious awards for his contribution to research in Respiratory Diseases

Presented by:
Alberta Respiratory Centre (ARC)
funding also provided by Grifols

THE DEAN’S LECTURE SERIES PROVIDES FUNDING TO DEPARTMENTS AND INSTITUTES TO SUPPORT THE VISIT OF INTERNATIONALLY RECOGNIZED LEADERS IN ANY AREA OF RELEVANT RESEARCH TO THE FOMD.
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Nano-Encapsulating of Sesquiterpenes Increase the Efficiency of Intracellular Delivery to Prevent Inflammatory Responses

Narcy Arizmendi\textsuperscript{a,c}, Marianna Kulka\textsuperscript{a,b,c}

\textsuperscript{a}Nanotechnology Research Centre, National Research Council Canada, Edmonton, AB, Canada. \textsuperscript{b}Department of Medical Microbiology and Immunology, and \textsuperscript{c}Alberta Respiratory Centre (ARC) Research, Department of Medicine, Faculty of Medicine, University of Alberta, Edmonton, AB, Canada.

\textbf{Introduction:} Biodegradable polymeric nanoparticles (NPs) have been used as drug delivery systems for natural and synthetic compounds, aiming to control the loading and release of biodegradable materials for use as immunotherapy to target cells, tissues and organs. Eremophilane-type sesquiterpenes are plant-derivate molecules that exhibit anti-allergic and anti-inflammatory properties in studies \textit{in vitro} and \textit{in vivo}. Controlled drug delivery of NPs encapsulating anti-inflammatory molecules would prevent, treat and reduce damage caused by inflammatory diseases. We aim to investigate whether NPs-plant derivate eremophilane-type sesquiterpenes increase the cell uptake, via inflammatory cell regulation of human mast cells (LAD2).

\textbf{Methods:} NPs synthesis was done using PLGA/PVA—sesquiterpene in a NanoAssemblr, NPs size distribution was evaluated by a Malvern Zetasizer and by transmission electron microscopy (TEM). Cellular uptake of NPs was analyzed by TEM and the anti-inflammatory responses were assessed by $\beta$-hexosaminidase and CCL-2 release by ELISA on LAD2 cells.

\textbf{Results:} NPs showed an average size of 60 to 70 nm. No cytotoxic effects were observed in LAD2 cells exposed to NPs, and we observed an inhibition in $\beta$-hexosaminidase and CCL-2 release. We present for the first time the synthesis of nanoparticles and sesquiterpene encapsulation (NPs), their cellular uptake and anti-inflammatory responses \textit{in vitro}.

\textbf{Conclusions:} Overall, our results suggest that NPs have the ability to inhibit human mast cell activation.
Introduction. Mast cells (MC) are major players in the immune system, acting as sentinels, responders and modulators of localized immune responses. MC are ubiquitously distributed in tissues and acquire local phenotypes, depending on the microenvironment. Upon activation, MC release a complex array of cytokines, chemokines and other immune modulators. The role of MC in cancer is anything but clear. In breast cancer, evidence indicates that infiltrating stromal MC may help reduce tumor growth, and increased MC numbers are associated with a favorable prognosis (Rajput et al., 2008, Breast Cancer Res Treat 107: 249-57; Dabiri et al., 2004, Mod Pathol 17: 690-5; Aaltomaa et al., 1993, Anticancer Res 13:785-8).

Methods. We hypothesized that immune mechanisms associated with the direct activation of tumor-associated MC can cause apoptosis of tumor cells and a reduction in tumor size. To test this, we used an orthotopic 4T1 mammary carcinoma mouse model. MC were activated by injecting the secretagogue compound 48/80 (c48/80; 50µg/kg body weight), or PBS (control group), into two peritumoral sites eight days after tumor implantation. We monitored tumour volumes and collected tumor tissues for histological analysis.

Results. Eleven days post-treatment with c48/80, average tumor volume in c48/80 mice (474±65 mm³, n=10) was significantly lower than control (827±49.9 mm³, p<0.001, n=11). Histological analysis of tumor tissues showed a greater number of apoptotic cells per field in the c48/80-treated group (10.95±0.93, p<0.0005, n=5) compared to control (4.79±0.45), 72 hours post-treatment. C48/80 was not toxic to 4T1 cells and it did not affect their production or release of factors such as stem cell factor (SCF), interleukin 3 (IL-3), tumor necrosis factor (TNF) or monocyte chemoattractant protein 1 (MCP-1).

Conclusions. Peritumoral MC activation showed significant anti-cancer effects, with decreased tumor size and increased tumor cell apoptosis. However, further studies are needed to elucidate the role of MC in breast cancer.

Funding provided by the Canadian Breast Cancer Foundation (CBCF) and the Canadian Institutes of Health Research (CIHR).
Cross-Sectional Analysis of the Occupational Health and Wellness of Alberta’s Unionized Insulators

Samineh Kamravaei,1 Kawtar Idrissi Machichi,1 Noushin Miandashti,1 Jennifer Spring,2 Linda Henderson,2 Meghan Dueck,1 Lei Pei,1 Fadi Khadour,2 Muhammad T. Naseem,2 Paige Lacy,1 Lyle Melenka2

1Alberta Respiratory Centre, Department of Medicine, University of Alberta, Edmonton, AB; 2Synergy Cardiac & Respiratory Care, Sherwood Park, AB

Introduction: Cardiovascular and respiratory diseases are among global leading causes of mortality. Insulators are at risk of these illnesses because of chronic exposure to hazardous insulating materials such as asbestos and silica, which have been shown to cause pulmonary and cardiovascular disease. In this study, we carried out a retrospective analysis of insulators and their health to determine if early detection and treatment of occupational exposure-related diseases were possible.

Methods: The Wellness of Workers program (WoW) has been established as a surveillance program for Alberta’s unionized insulators. Family lifestyle, health history (e.g. smoking habits, illnesses, etc.), and work history (specifically, insulation exposure) of insulators were identified using validated questionnaires. Validated tools were also used to calculate the Framingham cardiac risk score and COPD assessment test (CAT) score. Insulators underwent pulmonary function tests (PFTs), X-ray screening, and CT scans, if necessary.

Results: Since the beginning of the study in 2011 to December 2018, 894 insulators (average age of 45 ± 14 years) joined the WoW surveillance program, with an average trade experience of 16 ± 14 years. More than half of the cohort (63%) was exposed to asbestos through different applications, and 66% of the cohort had a history of smoking (i.e., current or ex-cigarette smoker). The average CAT score was 6 ± 6 (normal range of 0-10), and 17% of X-rays performed showed lung abnormalities. Asbestos-related lung diseases were observed in 9.4% of the cohort. The Framingham risk average score was 13% ± 11% (normal range of 0-10%), indicating an elevated risk of developing cardiovascular disease within the next 10 years.

Conclusions: Our findings show potentially serious health effects occurring in insulators who are chronically exposed to airborne particulate hazards while installing insulation in homes and businesses. Specifically, the current data demonstrates a lower level of lung and cardiac health in insulators. Our study is still in progress to increase the sample size and complete the longitudinal analysis to allow us to determine if early detection and treatment of insulators may be possible.
Pre-transplant Opioid Use Is Not Associated with Post-Transplant Survival in Lung Transplant Recipients

Sana Vahidy, David Li, Alim Hirji, Ali Kapasi, Justin Weinkauf, Dale Lien, Kieran Halloran

Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Introduction: The impact of opioid use in lung transplant (LTx) candidates on post-transplant outcomes is unknown. Previous studies on opioid therapy in kidney and liver transplant candidates have suggested increased risk of graft failure or death. We sought to test the association between pre-transplant opioid use in LTx candidates and overall retransplant-free survival.

Methods: We retrospectively reviewed patients transplanted between November 2004 - August 2015. The exposure was any opioid use at time of assessment. Our primary outcome was retransplant-free survival. Secondary outcomes included daily oral morphine equivalent (OME) dose in a Cox regression model, duration of ventilation, ICU and hospital LOS, 3 month and 1 year survival, and continuing use at 1 year.

Results: The prevalence of opioid use at assessment was 14% (61/425). Median daily OME dose was 31mg (18-54). Recipient race was associated with pre-transplant opioid use (Table 1). Opioid use was not associated with overall retransplant-free survival via log rank (p=0.08, Figure 1) [no change after excluding ventilation/ECMO bridging cases] or in a dose-dependent Cox model (HR 1.07 per OME [95%CI 0.12-4.55], p=0.94). All secondary outcomes were similar between groups except hospital LOS (opioid users 35 vs. non-opioid users 27 days, p=0.014). Continued opioid use in survivors at 1 year post-LTx was common (27/56, 48%).

Conclusions: Pre-transplant opioid use was not associated with overall post-transplant survival in our cohort and should not preclude listing. Further work stratifying opioid use by indication and the association with opioid use disorder would be worthwhile.
Improving Advance Care Planning for People with IPF

Diane Laverty, Kyle Whitfield, Meena Kalluri

Department of Medicine, University of Alberta, Edmonton, AB Canada

**Introduction:** People with chronic, life-limiting illnesses, such as idiopathic pulmonary fibrosis (IPF), are often not engaged in serious illness conversations, including advance care planning, and are unlikely to receive palliative care. Unfortunately, without these conversations many people experience acute, life-threatening events without communicating their wishes for care at the end of their lives. During these crises, caregivers may make critical decisions which do not align with a patient’s wishes or preferences, resulting in trauma for health care providers, patients and their supports.

To alleviate this situation, a tool was developed to encourage people with life-limiting illness and their supports to express their wishes and values in a non-threatening way, without the trigger of a definite, terminal prognosis. This study explored the acceptability and use of this tool for patients with IPF and their caregivers.

**Methods:** Two focus groups were hosted to evaluate the tool: one for patients and one for their caregivers. A follow up survey and interviews are in progress. Focus groups were audio-recorded after obtaining informed consent. The transcripts were analyzed using a thematic approach.

**Results:** Participants welcomed the tool and commented that it introduced a difficult topic in a gentle way. Participants, especially caregivers, expressed gratitude at the opportunity to share their thoughts.

Feedback about the tool included the need to ensure a positive focus and recommended minor. Discussions also addressed how they would use the tool. Participants recommended the use of the tool during their first visit to the ILD clinic.

**Conclusions:** The tool encouraged life conversations, and prepared patients and caregivers to start talking to their health care provider about their wishes and preferences for treatment in a non-threatening way.

Potential benefits include:

- Preparing patients and their support people for difficult health conversations
- Providing time, space and place reflection on wishes, fears, and values in a non-threatening way
- Initiating difficult conversations without the need to deliver medical information at the same time
- Providing information about patients’ wishes and preferences so appropriate treatment is provided at the right time and place

With this tool, patients and their support persons can reflect, discuss and document their goals in advance of the conversations with physicians, thereby decreasing needed time in a clinical environment.

We hypothesize this approach will increase implementation of advance care planning in outpatient care.
Comparison of MRC Breathlessness Scale to a Novel Multidimensional Dyspnea Scale (MDDS) for Clinical Use

Meena Kalluri¹, Jeffrey A. Bakal², Ting Wang³, Sarah Younus¹

¹Department of Medicine Pulmonary Division, University of Alberta, Edmonton, Alberta, Canada, ²Patient Health Outcomes and Clinical Effectiveness Unit, University of Alberta, Edmonton, Alberta, Canada, ³Alberta Health Services, Edmonton, Alberta, Canada

Introduction: MRC breathlessness grade (0-5) is frequently used in respiratory clinics to assess dyspnea. However, it does not quantify dyspnea itself; but measures perceived disability in a 5 point grading (none to almost complete incapacity). MRC lacks dimensions to capture day-to-day experience of dyspnea, including at rest and associated severity. A more comprehensive clinical assessment tool is needed. We developed a multidimensional dyspnea scale (MDDS) to measure dyspnea across activities of daily living, exercise and rest using a numeric rating scale (0-10) for each component. MDDS demonstrated feasibility of use over past 5 years.

Methods: Single center, retrospective observational cohort study describing the IPF dyspnea profile in patients seen at our ILD clinic (2012-18). Patients with both MRC and MDDS were included in the correlation. We compared MRC grade with MDDS at first visit, and measured their correlation. We also compared the 2 scales to 6 minute walk distance (6MWD), a common clinical measure of physical capacity.

Results: 93 IPF patient charts were reviewed; mean age 74 years (SD=9.7) with 66% males. Statistical analysis showed that the dressing component of MDDS and MRC grade were strongly correlated (n=10; r²=0.61). Other MDDS dimensions showed poor correlations, indicating these components of dyspnea are not being captured in the MRC grading: Sixty seven percent of MRC 3 patients reported dyspnea while resting and 76% while eating. Sixty two percent of grade 4 patients had dyspnea while resting and 76% while eating. 6MWD is a measure of physical capacity in ILD; when compared to MRC grades, similar to previous results, we show that higher the MRC grade, lower the 6MWD (r²=0.45). We then compared 6MWD to MDDS component scores, dressing (r²=0.55), stairs (r²=0.13) and light activity (r²=0.05).

Conclusions: MDDS allows further dyspnea characterization within each MRC cohort by adding clinically relevant dimensions and grading severity of breathlessness. These dimensions are not captured by MRC. MDDS facilitates recognition of heterogeneity of breathlessness experience, important for holistic dyspnea profiling and targeted therapies. Our previous work shows that the use of MDDS supports early identification and treatment of dyspnea in clinical practice (Kalluri, JPSM 2018). MRC 5 represents most disabled patients, presumably including those with dyspnea with resting and eating. However, we note that patients in MRC 3 and 4 grades also reported such type of dyspnea with MDDS.
Incidence and Significance of Thromboembolic Disease in Critically Ill Pulmonary TB Patients

Angela Lau, Wendy Sligl, James Barrie, Richard Long

Department of Medicine, University of Alberta, Edmonton, AB

Introduction: Pulmonary TB (PTB), even when advanced, does not usually cause serious respiratory impairment as ventilation and perfusion are reduced in parallel. We have been impressed by the frequency with which ventilator-dependent PTB patients are found to have pulmonary thromboemboli (PTE). Conceivably, the redistribution of pulmonary blood flow and PTE to intact lung in PTB contribute to respiratory failure and mortality. The aim of this study is to describe the incidence and significance of PTE in critically ill PTB patients, and raise awareness of this potentially serious complication which heretofore, to our knowledge, unreported in literature.

Methods: We reviewed the clinical, laboratory, and mycobacteriologic records of all cases of smear-positive pulmonary TB (PTB) admitted to the general systems ICU of the University of Alberta Hospital, between 2006-2016. Investigation for and presence of thromboembolic events were documented and outcomes reported.

Results: Over the 11 year period, 240 adult (age >17 years) smear-positive PTB cases were admitted to the University of Alberta Hospital, of which, a total of 20 (8.3%) were admitted to a general systems ICU. Computerized tomographic (CT) scans were performed in 10 cases and PTE was found in 5 (50%). One of these cases, and three others who had not undergone a CT had a deep venous thrombosis. Nine (45%) patients died during treatment (4 in ICU and 5 within 3 months of discharge from ICU). Mortality in patients with and without PTE, and with unknown PTE status were 2 (40%), 2 (40%), and 5 (50%), respectively.

Conclusions: TB is understood to cause a hypercoagulable state. The pathophysiologic defect in PTB would predict that PTE would cause serious gas exchange impairment. Our experience justifies this concern and supports the need to exclude thromboembolic events in ventilator-dependent PTB patients.
Does the Supine Position Normalize the Capillary Blood Volume and Diffusion Capacity Response to Exercise in Mild COPD?

Bryan Ross, Devin Phillips, Andrew Brotto, Desi Fuhr, Sean van Diepen, Tracey Bryan, Michael Stickland

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Introduction: Exertional dyspnea is a hallmark of Chronic Obstructive Pulmonary Disease (COPD) and is the primary reason for exercise intolerance even in mild airflow obstruction. A portion of the elevated dyspnea in mild COPD is due to inefficient ventilation. COPD patients demonstrate an elevated minute ventilation relative to CO₂ production (\(\dot{V}_E/\dot{V}_{\text{CO}_2}\)) during exercise, explained by increased deadspace ventilation. This may be due to inadequate capillary perfusion secondary to pulmonary vascular dysfunction or capillary destruction. We recently found that mild COPD patients demonstrate blunted capillary blood volume (\(V_c\)) and diffusion capacity (DLCO) responses to exercise, which was related to increased exercise \(\dot{V}_E/\dot{V}_{\text{CO}_2}\). Reduced \(V_c\) would be explained by either vascular dysfunction or capillary destruction. The supine position confers full capillary recruitment as blood is redistributed towards the thorax. It is unclear whether the blunted \(V_c\) response in mild COPD would be normalized with supine exercise, when alveolar-capillary units become better perfused as compared to upright exercise. The aim of this study is to examine the \(V_c\) response to supine exercise. We hypothesize that supine positioning will normalize the \(V_c\), DLCO and \(\dot{V}_E/\dot{V}_{\text{CO}_2}\) response to exercise in mild COPD.

Methods: In this randomized crossover study, 15 patients with mild COPD and 15 age and sex-matched control subjects will be recruited. On Day 1, each participant will undergo screening pulmonary function testing (PFT) and cardiopulmonary exercise testing (CPET). On Days 2 and 3, participants will be randomized to either upright or supine steady-state exercise at two intensities (40W and 60W upright, and the equivalent respective supine workloads). Multiple FiO₂ DLCO method will be used to determine DLCO, \(V_c\), and membrane diffusing capacity (\(D_m\)), both at rest and during exercise. Modified Borg dyspnea will be collected. \(\dot{V}_E/\dot{V}_{\text{CO}_2}\) will be calculated. Cardiac output and pulmonary artery systolic pressure (PASP) will be estimated by echocardiography.

Statistical analysis will be performed using two-way repeated measures ANOVA to evaluate the effect of position (supine versus upright) on the \(V_c\) response to exercise in COPD and controls.

Significance: There remains debate as to whether the observed blunted \(V_c\) response to exercise in mild COPD represents pulmonary vascular dysfunction (whereby arterioles are unable to appropriately regulate perfusion of alveolar-capillary units), or conversely, pulmonary vascular destruction (whereby alveolar-capillary units are obliterated). If the blunted \(V_c\) response to exercise corrects in the supine position it would suggest vascular dysfunction rather than destruction, and may thereby identify a therapeutic target for future work.
Episodic Breathlessness in Interstitial Lung Disease as Illustrated by a Multidimensional Dyspnea Scale (MDDS) in a Multidisciplinary Clinic

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Introduction: Dyspnea is a common, debilitating symptom in interstitial lung disease (ILD) that impairs quality of life. It is commonly underrecognized and undertreated. Episodic breathlessness (EB) has been recently defined as a “time-limited, severe worsening of intensity or unpleasantness of breathlessness in the patient’s perception” which can be either predictable or unpredictable [1]. EB prevalence is not yet reported on in an ILD population. There are no clinical scales to assess EB severity. MDDS is a novel, rest and activity-based dyspnea scale created for comprehensive dyspnea profiling in ILD patients and as a clinical decision aid for dyspnea management. Previous work showed that our multidisciplinary clinic’s care strategies, including use of MDDS, facilitate early recognition and treatment of dyspnea and reduce acute care utilization demonstrating the scale’s clinical utility. Here we report on baseline EB in ILD using MDDS.

Methods: This is a retrospective study of deceased ILD patients (2012-2018) seen at the University of Alberta multidisciplinary ILD clinic. Baseline MDDS (on a ten-point scale: 0 = no dyspnea and 10 = severe dyspnea) as well as other variables including age, gender, diagnosis, comorbidities, pulmonary function tests, 6-minute walk distance (6MWD) data and baseline MRC score were extracted and analyzed. EB was defined as an MDDS of ≥ 7/10 with any activity.

Results: Thirty-five charts with baseline data were identified. Median age was 75 years; 63% were male; 24 had idiopathic pulmonary fibrosis (IPF); 11 had other ILD. Comorbidities included: COPD 20%; Pulmonary Hypertension 25.7%; Cardiac Disease 37.1%; Anxiety 2.9% & Depression 17%. Median 6MWD was 281.35 meters (n=24) with 37.5% using oxygen; median FVC % predicted was 65.8% (n=27) and median % predicted DLCO Adj Hb was 42.82% (n=17). Median MRC was 4; median MDDS score was 1 with rest and 4 and 7 with low & moderate grade activity respectively. EB triggered by one or more activities was reported by 22 patients (63%) and 14% of patients reported unpredictable EB.

Conclusions: This is the first study to describe EB in ILD. EB is prevalent in ILD and should be included in dyspnea assessment. MDDS identifies EB and characterizes dyspnea severity. Our work has important clinical implications for EB treatment, such as recognizing the need for rapid acting opioids amenable to self-administration to match its’ profile. Routine EB assessment and appropriate treatment may improve symptom control and decrease acute care use in ILD.

References:
Introduction:  Idiopathic pulmonary fibrosis (IPF) is a fatal lung condition characterized by altered lung architecture and progressive respiratory failure.  Our multidisciplinary pulmonary clinic provides excellent symptom management and palliative measures throughout the disease course, from diagnosis until death.  As a result, we recognize that a growing population of patients with IPF now die at home, rather than in hospital.  Patients who die with IPF at home may have a distinct clinical or histopathological phenotype from those who require transfer to acute care, and this study aims to identify these differences.  In addition, we review the pathological features of IPF, and examine the complications of IPF which most commonly result in respiratory failure.  Furthermore, this study highlights the importance of autopsy in advancing understanding of disease processes.

Methods:  Patients with a pre-mortem diagnosis of IPF who died at home or in hospice and consented to autopsy were identified.  Lung tissue was analyzed by a subspecialized respiratory pathologist for typical pathologic features and respiratory complications of IPF.  Post-mortem phenotypes were compared to pre-mortem diagnoses, and complications were analyzed to determine the commonest phenotypes of IPF patients at death.  For patients who did not have autopsy limited to the heart and lungs, further analysis of other systems was performed.

Results:  Twenty patients with were identified for analysis.  The average age of death of patients enrolled was 72.5 years.  One hundred percent (100%) of patients had classic honeycombing architecture on post-mortem analysis, and 90% had lymphocytic inflammation.  Commonest complications included pulmonary hypertension (95%), pulmonary hemorrhage (80%), pulmonary edema (75%), broncholobar pneumonia (50%), diffuse alveolar damage (42%), and microscopic pulmonary emboli (40%).  Ten patients had analysis of extrapulmonary tissue, and of these thirty percent had evidence of esophageal fibrosis.

Conclusions:  This autopsy study demonstrates the most common causes of respiratory failure in a subset of patients with IPF who died at home.  The rate of diffuse alveolar damage was significantly lower in our population than in patients with IPF who die in hospital.  We hypothesize that excellent symptom management not only facilitates patients dying at home but may also decrease the risk of certain complications of IPF.  Additionally, this is the first documented study of pathologically confirmed esophageal fibrosis in patients with IPF.  This new finding may prove useful in better understanding the pathophysiology of IPF and serves as an exciting new ground for possible clinical interventions.
Advanced Care Planning (ACP) Model in Idiopathic Pulmonary Fibrosis

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**Introduction:** Advance Care Planning (ACP) is an interactive patient centered communication process between patients, their families and the health care team and is widely endorsed as integral to chronic respiratory disease management. Idiopathic Pulmonary Fibrosis (IPF) has a short median survival of 2-3 years, yet over 80% of patients with IPF do not have ACP discussions, and end up dying in hospital without any palliative care involvement. Barriers to ACP implementation include an unpredictable disease trajectory, care fragmentation, poor quality of communication, lack of healthcare professional (HCP) education and training, as well as time pressures in clinical practice. We reviewed the IPF-specific medical literature on ACP content and end-of-life (EOL) needs. Based on the results of this review, we further adapted ACP content for discussions in our outpatient clinic to facilitate patient wishes with respect to their care and death. Here, we describe our conceptual framework of ACP grounded in review of published qualitative literature on IPF.

**Methods:** We searched the published narrative literature on ACP needs in IPF to support our conceptual framework for IPF-specific ACP. Based on this review and our experience, we expanded our ACP framework content and process that we have been utilizing since starting our Multidisciplinary ILD Clinic in 2012.

**Results:** We identified 13 qualitative studies that interviewed patients, caregivers or sought opinion from patient advocacy bodies to understand the ACP needs in this population. The following needs were identified based on supporting quotes: (1) open, early and ongoing discussions, (2) the need for disease specific knowledge, (3) discussion on symptom control, (4) early caregiver involvement, (5) community resources for ongoing care, education & support. Based on published patient quotes and our experience, we not only document care preferences at EOL but emphasize living well now with discussion on how care will be delivered in locations of their choice to meet patient identified goals at EOL. We discuss symptom self-management and provision of community support for patients and caregivers to empower them.

**Conclusions:** Our ACP conceptual framework is grounded in rich qualitative data from the literature. We propose that our framework for ACP leads to meaningful and impactful ACP conversations that improves quality of life and death, supports EOL care and decreases unnecessary healthcare costs in IPF. Preliminary evidence using this framework in our Multidisciplinary ILD Clinic confirms feasibility, sustainability, and a positive impact on acute care utilization and greater adherence to patient wishes.
Effect of Inhaled Nitric Oxide on Maximal Oxygen Consumption in Healthy High- and Low-Fit Individuals

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Introduction: Emerging research has shown that the compliance of the pulmonary vasculature may be an important contributor to aerobic fitness as evaluated by maximal oxygen consumption (VO₂max). Our previous work suggests that endurance-trained athletes have a more compliant pulmonary vasculature as compared to untrained individuals, which may contribute their greater VO₂max. Inhaled nitric oxide (iNO) improves pulmonary vascular compliance at rest in healthy individuals, which may translate to greater compliance during exercise and improved VO₂max. The purpose of this study was to examine whether iNO improves VO₂max in high-fit and low-fit individuals. It was hypothesized that iNO will increase VO₂max in both groups, with the greatest effect observed in low-fit individuals with lower baseline pulmonary vascular function.

Methods: The study was a randomized double-blind cross-over design completed over three sessions: Day 1) participants completed a pulmonary function and standard cardiopulmonary exercise test (CPET). Low-fit was defined as a VO₂max between 30-45 mL/kg/min, and high-fit was defined as a VO₂max >55 mL/kg/min for females and >60 mL/kg/min for males. Days 2 and 3) participants completed a modified CPET while breathing either normoxia (placebo) or 40 parts per million of iNO (order randomized). Expired gas was collected to obtain VO₂, VCO₂, and ventilation. Cardiac output was estimated using impedance cardiography and systemic vascular conductance was calculated as cardiac output/mean arterial pressure.

Results: Seven high-fit individuals and four low-fit individuals have completed the study thus far. Compared to placebo, VO₂max was reduced while breathing iNO in the high-fit group (Placebo 70.1 ± 3.2 vs. iNO 67.0 ± 3.2 mL/kg/min, p=0.04), while VO₂max was unchanged between placebo and iNO in the low-fit group (p=0.71). Ventilation and VCO₂ were also unchanged in both high- and low-fit groups. Cardiac output was also unchanged with iNO in both high-fit (Placebo 17.5 ± 2.1 vs. iNO 20.8 ± 3.9 L/min, p=0.34) and low-fit groups (Placebo 13.9 ± 1.4 vs. iNO 14.9 ± 2.0 L/min, p=0.52).

Conclusion: Contrary to our original hypothesis, preliminary results demonstrate that iNO reduces VO₂max in the high-fit group, with no effect of iNO on VO₂max being observed in low-fit individuals.
Cells Mediating PAR-2 Activation in the Airways

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Introduction: Many aeroallergens have serine proteinase activity and may mediate their effects through proteinase-activated receptor 2 (PAR-2). Our lab demonstrated that, blocking PAR-2 activation on the airways, decreased allergic airway inflammation. Furthermore, Par-2 −/− mice develop attenuated airway inflammation with house dust mite (HDM) and ovalbumin mouse models of asthma indicating that, PAR-2 activation is essential for the development of allergic airway inflammation but, the exact cell/cells activated by PAR-2 activating proteinases in the airways is not clearly identified. We hypothesize that allergens possessing serine proteinases activity and/or endogenous proteinases, activate PAR-2 on airway epithelial cells, which induces the release of pro-inflammatory mediators and leads to allergic airway inflammation.

Methods: To understand whether the development of allergic airway inflammation requires PAR-2 expression on tissue resident cells (possibly airway epithelium) or hematopoietic cells we performed bone marrow (BM) chimeras between WT mice and Par-2 −/− mice. The chimeric mice were sensitized and challenged with Ovalbumin and airway inflammation was measured (number of eosinophils in bronchoalveolar lavage fluid). To investigate if we can induce airway inflammation in Par2 −/− mice by bypassing the required signal from activated PAR-2 on airway structural cells (possibly airway epithelium), we transferred CD4+ T cells from WT mice sensitized with HDM to naïve Par-2 −/− mice and WT mice. After transfer of CD4+ T cells the naïve Par-2 −/− and WT mice were challenged twice only by HDM and airway inflammation was measured.

Results: Par-2 −/− chimeric mice transplanted with WT BM cells developed attenuated airway inflammation similar to Par-2 −/− chimeric mice transplanted with Par-2 −/− BM cells. Also, we demonstrated reduction in allergic airway inflammation in WT chimeric mice transplanted with Par-2 −/− BM cells, however, the inflammation was twice the levels in Par-2 −/− chimeric mice transplanted with WT BM cells. Moreover, naïve Par-2 −/− mice injected with CD4+ T cells form HDM sensitized WT mice developed airway inflammation to the levels of WT mice after challenging twice with HDM.

Conclusions: Our results suggest that PAR-2 activation on tissue resident cells, possibly airway epithelial cells is indispensable for the development of airway inflammation, however, PAR-2 activation on hematopoietic cells also contributes to the development of the full effect. Signal from PAR-2 on structural cells, possibly airway epithelium is essential for sensitizing lymphocytes which is missing in case of Par-2 −/− mice and we can bypass this signal by transferring already sensitized lymphocytes to Par-2 −/− mice.
Vascular Implications of a Naturally Occurring Asthma Exacerbation

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Introduction: Asthma is a chronic inflammatory disease of the airways characterized by symptoms such as wheezing, coughing, chest tightness and shortness of breath. Individuals with asthma are at an increased risk of cardiovascular (CV) morbidity and mortality, yet the reason for this observation remains unclear. Vascular dysfunction is an early marker and predictor of future risk of CV disease, and can be the result of high levels of systemic inflammation. Pilot data from our laboratory indicate that asthma exacerbations lead to a significant increase in systemic inflammation. It is hypothesized that in addition to increased systemic inflammation, individuals experiencing an asthma exacerbation will have increased arterial stiffness and decreased endothelial function as compared to individuals with stable asthma and healthy controls.

Methods: In this cohort study, patients aged 18-55 (n=44) who present to the emergency department for asthma exacerbations will be recruited. All participants will receive standard emergency care for their asthma. Once stabilized, ultrasound imaging of the brachial artery and carotid-radial pulse wave velocity will be used to assess vascular function and arterial stiffness, respectively. Lastly, a venous blood sample will be obtained for systemic analysis of C-reactive protein, eosinophils, and neutrophils. Participants will return 48 hours after the exacerbation to complete the same assessments with the addition of spirometry as well as three questionnaires: The Asthma Quality of Life Questionnaire, the Asthma Control Questionnaire, and the EQ-5D. Participants will then be provided with a Fitbit to wear for 7 days to monitor daily physical activity. Data collection will be repeated 14 days following the exacerbation with the addition of a full pulmonary function test. Age and sex-matched healthy controls (n=44), and stable asthma controls (n=44) will undergo the same assessments at two time points, 48 hours apart.

Anticipated Results: Preliminary data (n = 16) has revealed C-reactive protein levels during an asthma exacerbation (6.8 ± 5.9 mg/L) are significantly elevated compared to stable asthma (3.0 ± 2.8 mg/L) and healthy controls (1.2 ± 2.8 mg/L).

Significance: This will be the first study to investigate the impact of an asthma exacerbation on vascular function and systemic inflammation. Should a naturally occurring asthma exacerbation be associated with vascular dysfunction, in addition to this observed systemic inflammation, this would advance our understanding of the clinical link for the increased CV risk observed with an asthma exacerbation.
Dose-dependent Association of Infant Antibiotic Exposure and the Gut Microbiota Composition at 12 Months of Age


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Introduction: Greater prescribing of antibiotics to infants has coincided with an epidemic of allergic diseases such as asthma in developed countries. Asthma is a respiratory disorder characterized by chronic airway inflammation and hyper-responsiveness that leads to episodic airflow obstruction. Infant antibiotic exposure, as well as gut microbiota composition, are linked to future risk of asthma. Stronger association observed with multiple courses of antibiotics and asthma add to biological plausibility. The relationship between early life antibiotics and later childhood allergic diseases may be explained by a disturbed gut microbiota. The purpose of this study was to determine the dose-response association between antibiotic exposure and gut microbiota composition in 12-month-old infants.

Methods: This study included a representative sample of full-term infants (n=190) in Manitoba from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Infant antibiotic exposure was obtained from hospital records (maternal intrapartum, newborn) and the provincial prescription database (infant). Birth method was obtained from hospital records. Fecal samples were collected at 12 months, and gut microbiota were profiled using illumina 16S rRNA gene sequencing. Spearman’s correlation was used to measure the strength and direction of association between number of antibiotic courses and median abundance of gut microbiota.

Results: About 61% of infants had been exposed to antibiotics during their first year of life and over 12% had received 3 or more courses. Maternal intrapartum and intravenous administration to the newborn considered as the first antibiotic course, accounted for 47% of antibiotic exposure. As the number of antibiotic courses increased, the median abundance of genus Streptococcus, Dorea and Lachnobacterium was observed to rise successively in gut microbiota. After stratification by birth method, more statistically-significant dose-related associations were observed in vaginally-born infants, seen as increased levels of Lachnobacterium (Spearman’s correlation(r) = 0.20; p = 0.02) and decreased abundance of Clostridia (r = -0.22; p = 0.01), Bacteroides and Ruminococcus. In caesarean-delivered infants, Blautia and Ruminococcus were observed to decrease in abundance with antibiotic dose.

Conclusions: Multiple courses of antibiotics affect gut microbiota composition and this association is more pronounced in vaginally-born infants. Dose-dependent associations have been reported between antibiotics and childhood asthma and allergic diseases. Hence, affected gut microbes may play an important role in infant immunity and health outcomes.
The Effect of Inhaled Nitric Oxide on Dyspnea and Exercise Capacity in Mild COPD


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Introduction: Patients with mild COPD have an exaggerated ventilatory response to exercise, contributing to exertional dyspnea and exercise intolerance, however, the reasons are not well understood. Our recent work has demonstrated a blunted pulmonary capillary blood volume response to exercise in mild COPD. Importantly, the low pulmonary capillary blood volume was associated with an increased ventilatory equivalent to carbon dioxide production ($V_E/V_{CO2}$) during exercise, suggesting that low pulmonary perfusion leads to excess ventilation (e.g., deadspace). Inhaled nitric oxide (NO) is commonly used to increase NO bioavailability, and improve pulmonary vascular function. If inhaled NO can increase perfusion in mild COPD, this would reduce $V_E/V_{CO2}$, dyspnea, and improve exercise capacity. The aim of this study was to examine the effect of inhaled NO on ventilation, dyspnea and exercise capacity in patients with mild COPD.

Methods: After completion of a standard pulmonary function and cardiopulmonary exercise test (CPET), 10 patients to date with mild COPD (FEV1/FVC ratio <0.70 and FEV1 ≥ 80% predicted) completed a randomized double-blind crossover study of experimental CPETs while either breathing normoxia (placebo) or 40 parts per million inhaled nitric oxide (iNO). Peak power output was defined as the greatest work rate that patients were able to maintain for at least 30 s. $V_E/V_{CO2}$ and $VO_2$ were evaluated using expired gas data and dyspnea was evaluated using a modified Borg scale. Cardiac output was estimated by impedance cardiography and systemic vascular conductance was calculated as cardiac output/mean arterial pressure.

Results: Experimental iNO increased peak power output (98 ± 7 vs. 112 ± 8 Watts, p=0.009) and peak oxygen uptake (1.53 ± 0.10 vs 1.77 ± 0.14 L/min, p=0.026), compared to placebo. At the highest equivalent work rate of 60 Watts, iNO reduced $V_E/V_{CO2}$ (35.6 ± 1.4 vs 32.0 ± 0.9, p=0.008) and dyspnea (3.5 ± 0.3 vs 2.4 ± 0.3 Borg units, p=0.003). At rest and during exercise, both cardiac output and vascular conductance were unaffected by iNO.

Conclusions: In a randomized controlled cross-over trial, iNO increased exercise capacity, secondary to an improvement in ventilatory efficiency (e.g., lower $V_E/V_{CO2}$) and reduced exertional dyspnea in patients with mild COPD. These data suggest that the elevated $V_E/V_{CO2}$, typically observed in mild COPD, may be secondary to pulmonary vascular dysfunction.
Deciphering the Amino Acid Agonists of Mast Cell MRGPRX2 Receptor

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Introduction: Mast cells play an important role in innate immunity. Upon activation, they degranulate and release bioactive agents into the local extracellular environment. Two extensively studied receptors which are involved in mast cell activation and degranulation are IgE dependent FcεRI and KIT receptor. Mast cells, however, are also activated in an IgE independent fashion through a class of G-protein coupled receptors called mas-related G-protein coupled receptor (MRGPRX2). The aim of our present work was to understand the nature and sequence of amino acids that can activate mast cells through MRGPRX2 receptor.

Methods: Proadrenomedullin N-terminal 20 peptide (PAMP-20) and its analogue PAMP-12 are endogenous peptides that activate mast cells specifically through the MRGPRX2 receptor. Using alanine scanning, N-terminal, and C-terminal truncation, a library of peptides was designed and tested on MRGPRX2 expressing HEK cells. Based on these results, various synthetic peptides were also designed and tested to understand the nature of amino acids that could activate mast cells. In a typical experiment cells were loaded with Fura-2, a calcium sensitive dye to determine intracellular calcium release upon activation by the designed peptides. The ratio of the fluorescence intensity at 510 nm relative to excitation wavelengths of 340 and 380 nm was calculated. The experiment was conducted with n ≥ 3. A concentration dependent study was also conducted for the designed peptides.

Results: It was found that peptide sequences FRKKW and WNKWAL had the same activation potential as PAMP-12. Removal of phenylalanine from the N-terminal showed a decrease in activation. The ratio also decreased for truncated peptides beyond the 5th position tryptophan from N-terminal during C-terminal and N-terminal truncation.

Conclusion: Understanding mast cell activation is imperative to the design of new therapeutics which may treat allergic reactions. We in this study have taken PAMP-12 as a model MRGPRX2 stimulant and tried to elucidate the underlying nature and structure of amino acids responsible for activation. Peptide sequences FRKKW and WNKWAL could activate mast cells as equivalent to PAMP-12. They could be considered the core motif of PAMP-12. The results also show that an N-terminal hydrophobic residue is crucial to mast cell activation, with aromatic bearing amino acids being of particular importance.
Introduction: Antibodies are powerful tools as they can bind to specific molecules and provide insightful information. Our previous research showed that rat protein Submandibular rat 1 (rSMR1) is under Autonomic Nervous System control and has an anti-inflammatory heptapeptide (SGP-T). However, humans do not produce SMR1. In our search for possible human candidates with sequences similar to SGP-T, we found hCABS1. To study hCABS1, we generated four polyclonal antibodies (pAb) to two 14-mer polypeptides in the protein. Antibodies H2.0, H2.1 & H2.2 were raised against a middle sequence. Antibody H1.0 against a sequence near the carboxy-terminus containing a putative analog of SGP-T. In Western blot (WB) analyses of saliva, H2.0 detects a positive correlation between hCABS1 levels and acute psychological stress. We have characterized all antibodies in WB, a novel capillary-based platform (Wes), and immunohistochemical analyses (IHC) of human submandibular gland (hSMG). Ongoing studies focus on the use of Wes to test if we can validate and extend previous data on hCABS1 as a biomarker of stress.

Methods: We tested specificity of our antibodies in WB by analyzing an hCABS1 overexpression cell lysate (OEL) and a negative cell lysate (NCL), and subsequent Mass Spectrometry (MS) analyses to verify the presence/absence of hCABS1. In Wes, we optimized the analyses with OEL, NCL and saliva, and are now testing saliva from a cohort of stress-exposed individuals. IHC were done using sections of hSMG, our four antibodies, labelled secondary antibodies, and relevant controls.

Results: Analyses of OEL and NCL in WB indicate that H2.0, H2.1 & H2.2 recognize both CABS1 (confirmed by MS) and another protein(s). H1.0 is specific to hCABS1. Wes immunoassay shows specific immunoreactivity to OEL, congruent with MS, and no immunoreactivity with NCL. Saliva analyses in Wes show that H2.0, that previously detected stress-induced changes in hCABS1 salivary levels, produces a different pattern than all other hCABS1 pAbs. IHC of hSMG show that hCABS1 is found in the salivary gland epithelium; moreover, H2.0 and H2.2 detect hCABS1 at basal epithelial duct cells.

Conclusions: Our data suggests that Wes is more specific than WB, favouring our decision to transition into Wes as a high-throughput, quantitative assay of hCABS1 levels in saliva. Furthermore, because of H2.0’s uniqueness and H1.0’s specificity, we will use them to analyze saliva samples from stressed individuals. Finally, IHC confirmation of the presence of hCABS1 in hSMG provides fuel for future studies of the physiological functions of hCABS1.

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The Effect of Etonogestrel on Ventilation in Adult Female Rats

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Introduction: For decades it has been known that progesterone acts both centrally and peripherally as a respiratory stimulant, as women who are in the luteal phase of their menstrual cycle or during pregnancy experience periods of hyperventilation, and post-menopausal women display an increased frequency of sleep disordered breathing compared to pre-menopausal women.

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder caused by a mutation of the transcription factor PHOX2B. Individuals affected by CCHS generally display normal breathing while awake however, suffer from a severe depression in breathing and increased endTidal CO2 levels mainly during nREM sleep.

There is no effective cure for the disease and the only option for treatment is mechanical ventilation or diaphragm pacing. Respiratory stimulants have proven ineffective, with the exception of a recent report that indicated a 2-3 fold increase in the ventilatory response to hypercapnia in two adult female CCHS patients. This response was observed with the onset of desogestrel intake, a potent progestin used as contraceptive. Thus, the use of progestins may have a respiratory stimulant effect on chemosensitivity,

In this study we tested the hypothesis that etonogestrel (ETO; the active metabolite of desogestrel) stimulates progesterone receptor expressing neurons to increase ventilation and the ventilatory response to hypoxia (HVR) and hypercapnia (HcVR) in healthy rats and recover the ventilatory response in impaired rats.

Methods: Healthy and chemosensitive impaired adult female rats were instrumented with implants to chronically deliver ETO over a four-week period. Rats were tested weekly in whole-body plethysmographs to determine changes in respiratory parameters (frequency, tidal volume, and minute ventilation) during baseline conditions (normoxia) and respiratory challenges (HVR and HcVR). At the end of the treatment period the response to hypoxia and hypercapnia was also tested under isofluorane anesthesia.

Results: Our results in healthy rats indicate that ETO does not affect the HcVR or HVR in freely behaving healthy female rats. However, ETO induced potentiation of ventilation in the second phase of the HVR under isofluorane anesthesia.

Conclusion: We observed little effect of ETO on ventilation in adult female rats in normoxia or under hypoxia and hypercapnia challenges. We will further investigate the effects of ETO on a rodent model of impaired chemosensitivity.
Routine Use of Post-Bronchodilator Testing in Pulmonary Function Testing Labs

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Introduction: Pulmonary Function Tests (PFTs) including spirometry with and without post-bronchodilator (post-BD) testing are frequently performed in the assessment of asthma, along with other obstructive airway disorders. Multiple publications over the past 15 years have noted that 1 in 3 physician-diagnosed asthma cases are not in fact asthma. In this quality assurance project, we assess whether PFT labs in Alberta have policies on post-BD testing, as extraneous and unnecessary use of post-BD testing can lead to wasted staff time, patient time and unnecessary expenses to the health care system.

Methods: We reviewed, in collaboration with the (College of Physicians and Surgeons of Alberta) CPSA and Alberta Medical Association (AMA), all PFT labs in the province of Alberta (hospital-based private not-for-profit [NFP] or “public” labs and private for-profit [FP] labs). This health policy study of PFT labs involved identifying the proportions and regional distribution of private NFP and private FP labs in the province of Alberta while assessing post-BD policies. Each PFT lab was asked for their policy regarding spirometry and asthma diagnosis from May 01 to August 31, 2017.

Results: A total of 92 PFT labs were identified in Alberta, 74 of which were private FP (independent) labs, while 18 were private NFP (public) hospital-based labs. Policies were captured according to the following: (i) Post-BD policy existed (and if so routinely performed / not routinely done); (ii) no post-BD policy; (iii) lab chose not to participate. All 18 hospital labs responded: 10 had no policy; 6 had a policy or algorithm; 1 did not perform post-BD testing (exercise testing), and 1 had multiple testing sites. Of the private FP labs, 3 had relevant policies and/or algorithm, 10 had none, and 61 provided no information. Access to PFT labs in Northern Alberta was sparse.

Conclusions: PFT lab policies surrounding post-BD testing were found to be heterogeneous in Alberta. Low response rates despite use of a systems approach and requests in writing and in person from FP labs were notable. Development of a standardized policy across the province would be beneficial. Further higher-level review of the appropriateness of post-BD use in both FP and NFP PFT labs is needed.

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Trafficking of the Th2 Cytokines IL-9 and IL-13 in Eosinophils

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Introduction: Approximately half of all patients with asthma are afflicted by eosinophilic inflammation in their airways. Eosinophils are highly granulated white blood cells that secrete pro-inflammatory cytokines, including interleukin-9 (IL-9) and interleukin-13 (IL-13). The intracellular sites of storage of IL-9 and IL-13 and mechanisms associated with their release are unknown. Here, we hypothesize that IL-9 and IL-13 are found as pre-formed cytokines stored in eosinophil crystalloid granules and other intracellular organelles.

Methods: Human peripheral blood eosinophils were purified from the venous blood of mildly eosinophilic volunteers by MACSxpress. Eosinophils were adhered to glass coverslips and stimulated with 5 μM platelet activating factor (PAF), a potent secretagogue. Cells were immunolabeled with antibodies specific to IL-9 or IL-13 and colocalized with markers for secretory organelles (CD63 for crystalloid granules, transferrin receptor (TfnRc) for recycling endosomes). We imaged cells using Deltavision OMX super resolution microscopy and quantified colocalization by Pearson’s correlation coefficient using Volocity. We created a protocol for automated colocalization, which generated similar results to manual colocalization, and applied this approach.

Results: Colocalization of IL-9 and CD63 significantly increased from 0.50 ± 0.01 to 0.57 ± 0.02 after 5 min of PAF stimulation, but decreased to 0.45 ± 0.01 after 60 min (p < 0.01). However, colocalization with IL-13 with CD63 was 0.37 ± 0.01, with no significant changes in resting vs stimulated cells. Colocalization of IL-9 with TfnRc increased from 0.47 ± 0.01 to 0.56 ± 0.01 after 5 min PAF stimulation, and continued to increase to 0.60 ± 0.008 after 60 min (p < 0.0001). In contrast, colocalization of IL-13 with TfnRc increased following 5 min stimulation from 0.41 ± 0.02 to 0.43 ± 0.01 (p < 0.001), but then decreased to 0.39 ± 0.01 (p < 0.05) after 60 min.

Conclusions: These results indicate that both IL-9 and IL-13 are stored in crystalloid granules, while only IL-9 is released using TfnRc recycling endosomes. Understanding the mechanisms involved in IL-9 and IL-13 release will contribute to our understanding of cytokine secretion, and coordinated efforts will link mechanistic understanding of cytokine release with clinical practice in treating patients with eosinophilic asthma. Current findings combined with future studies will provide insight into potential targets for pharmaceutical intervention.
Facilitating Factors for Home and Hospice Deaths in ILD Patients

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Introduction: Interstitial Lung Disease (ILD) is a heterogeneous group of fibrotic lung diseases characterized by poor EOL care and hospital deaths (80-100%) despite patient preferences for home deaths. ILD home deaths are rarely reported (0-14%). In 2012, we reorganized ILD care delivery through our multidisciplinary collaborative (MDC) ILD clinic to achieve patient preference for location of death as a marker of good quality EOL care. We examine patient, caregiver and care delivery factors associated with home or hospice deaths in our cohort, hypothesizing that an early, integrated palliative approach can improve EOL care delivery and align location of death with patient preferences.

Methods: Electronic records of deceased ILD patients who received care at the University of Alberta MDC ILD clinic (Nov’12- Aug’18) were reviewed; patient, caregiver and care delivery data were extracted and analyzed using descriptive statistics.

Results: Twenty-eight patients (37%) had home or hospice deaths (22 home, 6 hospice). The mean age at death was 77 years, 54% were male, 21 (75%) had IPF and 7 (25%) had non-IPF diagnoses. Twenty-six patients (93%) were willing and able to discuss advanced care planning (ACP) in clinic. 100% preferred home deaths (n=17). All patients had live-in caregivers at the time of death; 86% of caregivers were engaged in ACP at clinic visits. Care components included: (1) Symptom self-management discussed with 27 patients (96%) a median of 278 days before death, (2) Opiates for dyspnea were administered to 25 patients (89%) a median of 78 days before death, (3) ACP was initiated in 26 patients (93%) a median of 178 days before death, (4) Home care referral was noted in 26 patients (93%) a median of 156 days before death and (5) Home visits by a healthcare professional within 1 month of death were noted in 15 patients (n=16) (94%), (6) Formal palliative care consultation was noted in 6 patients (21%).

Conclusions: Home & hospice deaths are feasible in ILD. We identify several patient, caregiver and care delivery factors associated with home or hospice deaths. Early initiation of various palliative care components such as ACP discussions, symptom self-management; caregiver engagement and close collaboration with community supports can promote adherence to patient preference for home or hospice deaths. Health care professionals require training in palliative approaches and supportive resources must become widely available.
Significance of Asymptomatic Oxygen Desaturation in Elderly ED patients: A Pilot Study

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Introduction: Pulse oximetry is a standard component of Emergency Department (ED) triage and patient monitoring. Pulse oximetry measures peripheral capillary oxygen saturation (SpO2) levels and can be used to monitor cardiorespiratory conditions. The normal SpO2 level for adults is approximately 96%. Oxygen saturations of <92% are considered problematic by emergency physicians and levels <90% may indicate significant cardiorespiratory disease. However, relatively low oxygen saturations are often seen in elderly patients with comorbidities. This research investigated the significance of hypoxia in asymptomatic older ED patients with no apparent acute illness.

Methods: ED patients >75 years with a documented room air pulse oximetry reading <92% were eligible for study. Exclusion criteria included dyspnea, chest pain, SBP<100mmHg, HR>120 or <50; sustained tachypnea (RR>20); admission for an acute cardiopulmonary condition, delirium or acutely altered mentation. Eligible patients who consented to participate were separated into two groups: 1) Sustained asymptomatic hypoxia: two or more SpO2 readings <92% 2) Unsustained asymptomatic hypoxia: one SpO2 reading <92%. 30-day adverse events were tracked using a Sunrise Emergency Care record review. Adverse outcomes investigated included death, MI, CHF, PE, cardioversion, ICU admission, intubation, NIV, ED revisit or re-hospitalization. Patient characteristics investigated included age, sex, arrival mode, triage complaint, CTAS level, pulse, BP, RR, weight, residence (independent, assisted living, facility), comorbidities, PHN, referral, disposition, and test results if performed (CXR, troponin, ECG, CT). Follow-up phone calls were completed after 30 days to assess patient status and confirm ED revisit, readmission, ICU stay, outcome event or diagnosis.

Results: A total of 876 ED patients >75 years were screened. Of these patients, 100 met the study criteria and 56 patients consented to participate. 30-day follow-up data was analyzed for 34 enrolled patients. The sustained hypoxia group (n=23) showed higher rates of experiencing 30-day adverse outcomes of death, ED re-visitation, MI, CHF, a severe episode of COPD, PE and ICU stays compared to the unsustained hypoxia group (n=11).

Conclusions: Conclusions are preliminary and data analysis for 22 patients is ongoing. ED re-visits, incidences of cardiorespiratory complications, and mortality were significant in discharged sustained hypoxic patients, especially if O2 sat <90%. Pulse oximetry assessment of oxygen saturation in seniors’ care facilities and physicians’ offices may be important in screening for future adverse health outcomes in elderly patients.
Lung Height Measurements via Chest X-Ray for Donor-Recipient Size Matching in Lung Transplantation

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Introduction: Donor to recipient lung size matching has been shown to augment the risk of primary graft dysfunction (PGD) following lung transplantation. The most common assessment for size matching is the ratio between donor and recipient predicted total lung capacity (TLC) but this method does not consider the recipient’s intrinsic lung disease, which can substantially change lung volumes. The utility of chest x-ray (CXR) measurements to size-match donors with recipients is not known. We hypothesized that CXR size measurements could serve as a surrogate marker of the actual donor and recipient TLC and that mismatches would be associated with PGD risk.

Methods: We conducted a retrospective cohort study of adult double lung transplant recipients at UAH from 2007-2016 for whom donor CXRs were available. We reviewed pre-transplant recipient and donor CXRs and measured lung heights using digital calipers to determine two measurements: lung apex to mid-hemidiaphragm (AMD) distance and apex to costophrenic angle (ACPA) distance, then took the mean value of the left and right lung. For donors, we used the largest set of measurements from the 3 most recent CXRs, while for recipients, we measured the immediate pre-transplant CXR. The primary outcome was the development of grade 3 PGD (lung edema and PaO2/FiO2 < 200 mmHg) at 48 or 72 hours post-transplant. “Oversizing” was defined as donor-to-recipient lung height ratio > 1 and “undersizing” ≤ 1. We used logistic regression to assess the relationship between size matching via lung height ratio and grade 3 PGD, adjusting for donor age and lung ischemic time.

Results: 206 patients met inclusion criteria, 32 (16%) of whom developed grade 3 PGD at 48/72 hours. AMD and ACPA values for the same patient were highly correlated and we elected to use ACPA as our main measurement. Recipient ACPA strongly correlated with recipient actual TLC (0.84, p < 0.0001). Oversizing (ACPA ratio > 1) was associated with increased risk of grade 3 PGD in both unadjusted and adjusted models (unadjusted OR 2.5 [1.2-5.4], p = 0.02; adjusted OR 2.3 [1.0-5.2], p = 0.04).

Conclusions: Oversizing as determined by CXR measurements was associated with increased risk of grade 3 PGD. Our CXR measurements were highly predictive of actual recipient TLC, thus inherently accounting for volume changes related to the underlying lung disease in contrast to pTLC which does not. We propose ACPA ratio as a valid size matching tool in donor allocation.
Persistent Atelectasis Following Primary Graft Dysfunction is Associated with Lower Lung Function in Lung Transplant Recipients

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Introduction: Primary graft dysfunction (PGD) is the most important contributor to early mortality in lung transplant recipients and has also been associated with lower lung function and impaired overall survival. We assessed radiographic features on 3-month post-transplant lung computed tomography (CT) scans of lung transplant recipients, as well as the association between these features and long-term lung function. We hypothesized that radiographic abnormalities would be more frequent in PGD survivors and mediate poorer lung function.

Methods: We conducted a retrospective cohort study of adult double lung transplant recipients at UAH from 2010-2016 for whom 3-months CT scans and 1-year lung function data was available. Grade 3 PGD was defined as the presence of lung edema on post-operative CXR and PaO2/FiO2 < 200 mmHg at 48 or 72 hours post-transplant. The primary outcome was the presence of 3-months post-transplant CT abnormalities including: pleural effusion, ground glass opacification, centrilobular opacification, interlobular septal thickening, atelectasis, consolidation, fibrosis, and air trapping. We also assessed 3-months bronchoscopic microbiology data to account for associations related to this. We classified radiographic abnormalities as ranked ordinal variables based on the number of involved lobes. We used Cochran Armitage trend testing to assess the relationship between PGD development and radiographic changes. We used a multivariable linear regression to model the impact of radiographic abnormalities on 1-year forced expiratory volume in 1 second (FEV1), controlling for grade 3 PGD (PGD3).

Results: 237 patients met inclusion criteria, 50 (21%) of whom had developed PGD3 at 48 or 72 hours. Amongst all CT abnormalities, PGD3 was associated with more frequent or more widely distributed interlobular septal thickening (p = 0.0389) and atelectasis (p < 0.0001) at 3 months. There was no relationship between the presence of clinically relevant bacteria or fungi on 3-months bronchoscopies and any radiographic abnormality. Patients who developed grade 3 PGD had lower 1-year FEV1 % predicted than patients without PGD3 (76 ± 23% vs. 86 ± 21%, p = 0.014), but in a multivariable model with atelectasis (validated as a linear variable) and PGD3, only atelectasis remained significantly associated with 1-year FEV1 % predicted (p=0.0088).

Conclusions: Grade 3 PGD is associated with increased interlobular septal thickening and atelectasis on 3-month post-transplant CT. Atelectasis appears to function as a mediator of lower lung function at 1 year in PGD survivors. This may suggest a role for persistent surfactant and type II pneumocyte dysfunction in post-PGD lungs.
The Impact of Changes in Weight on Pulmonary Function Post-Lung Transplantation

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Introduction: Weight gain post-lung transplantation is an increasingly common problem. An increase in weight in the abdomen or chest regions is a known cause of extra-pulmonary restriction, and may lead to a decline in lung function in the obese population. We postulate that patients with significant weight gain post-lung transplant have a concomitant decline in lung function.

Methods: We performed a retrospective study of patients transplanted at the University of Alberta Hospital from January 2006 to December 2015. Baseline characteristics, weight and both forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were collected at serial surveillance spirometry tests post-transplant. Patients under the age of 16 years were excluded from the study. A linear mixed effects model was performed to assess the impact of weight on lung function, and was adjusted for age, sex, diagnosis at listing and body mass index (BMI) at transplant.

Results: During the study period, 434 eligible lung transplant recipients had available serial lung function data, with a total of 17035 spirometry reports. In patients who did not develop obesity post-transplant (BMI ≥ 30 kg/m²), for every kilogram (kg) of weight gain, FEV1 increased by 0.016 liters (L) (0.014 - 0.016, p<0.001), while FVC increased by 0.034L (0.032 - 0.038, p<0.001). In 90 recipients who developed obesity post-transplant, there was a significant interaction between weight and both FEV1 [-0.0142 (-0.0174 – -0.0110), p<0.001] and FVC [-0.0203 (-0.0239 – -0.0167), p<0.001]. Therefore, this cohort did not see any clinically significant changes to FEV1 in response to weight (0.001L/kg), and only 0.014L/kg in FVC. Patients whose weight increased to ≥ 30 kg/m² had lower overall FEV1 [0.258L (0.510 - 0.006), p=0.04] and FVC [0.452L (0.740 - 0.164), p=0.002] compared to patients who did not develop obesity. For each point increase in BMI at time of transplant, overall FEV1 decreased by 0.046L (0.061 - 0.11, p<0.001), and FVC decreased by 0.073L (0.088- 0.054, p<0.001).

Conclusion: Post-lung transplantation, patients begin to gain weight and lung function increases as they rehabilitate. Lung function improves to a lesser extent in patients who become obese. Patients who became obese had lower overall FEV1 and FVC compared to patients who never cross over a BMI of 30kg/m². Finally, for every point increase in BMI at time of transplant, there are significant decreases in overall FEV1 and FVC.
Asthma and Youth Soccer: An Investigation into the Level of Asthma Awareness and Training Among Youth Soccer Coaches

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**Introduction:** Asthma is the most common chronic disease amongst children. Exercise-induced bronchoconstriction which is common in asthmatic patients, also occurs in individuals with no prior asthma diagnosis. Despite this and the fact that soccer is a high ventilation sport, there are no validated asthma management protocols in place for soccer coaches. This study aims to address 1) soccer coaches’ current knowledge on asthma, 2) whether there is a need for asthma related training, and 3) any barriers to administration of such training. We hypothesize that soccer coaches will have low levels of knowledge regarding asthma attack prevention/treatment and have received little to no asthma-related training, there is a need for asthma-related training, and there will be some barriers to administration of asthma training due to coaches’ negative attitude regarding asthma.

**Methods:** 2300 volunteer youth soccer coaches from the Edmonton Minor Soccer Association (EMSA) were invited to participate in completing a 22-question online survey. The survey was open for one month from June 8, 2018 to July 8, 2018. Responses were analyzed initially using descriptive statistical analysis, followed by chi-square analysis to study comparisons between responses to different questions.

**Results:** There was a response rate of 22% (513 of 2300). Respondents were on average, inexperienced coaches, coached younger age groups, and approximately one third of respondents had personal experience with asthma (either themselves or their child had asthma). 93% of respondents had not received any asthma-related training at any coaching level, whether it be from EMSA or the Alberta Soccer Association. Coaches had strong knowledge on how to treat asthma attacks, but mixed levels of knowledge on asthma attack prevention. Experienced coaches were better at identifying the number of players with asthma on their team and the number of asthma-related incidents they had encountered as coaches. Coaches demonstrated a receptive attitude towards receiving asthma-related training, with 91% of respondents saying training would be beneficial and 69% of respondents saying training should be mandatory.

**Conclusion:** The results of this study indicate that soccer coaches have limited knowledge regarding asthma management, acknowledge a need for asthma-related training, and are willing to participate in and could benefit from educational interventions as it pertains to their roles as coaches.
Regulation of Proteinase-Activated Receptor-2 in Airway Epithelial Cells

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Introduction: Proteinase-activated receptors (PARs), when activated by serine proteases, play a role in innate immunity through the regulation and release of pro-inflammatory mediators. PAR-2 is expressed on airway epithelial cells (ECs) where it can detect components of harmful inhaled particles, including allergens. PAR-2 has been implicated in the development of allergic asthma, as well its expression is increased in the airway ECs of patients with asthma. We hypothesize that endogenous and exogenous inflammatory stimuli regulate PAR-2 expression in airway ECs.

Methods: BEAS-2B cells, a transformed human bronchial EC line, were grown until confluent. They were then transferred to media without growth factors (starvation media) for 24 hours before being activated for another 24 h with different stimuli. Then RNA was extracted (TRIzol method) and reverse transcribed. RT-qPCR for PAR-2 and GAPDH (housekeeping gene) mRNA was then performed using a fluorescent probe method.

Results: IL-13 (20 ng/ml) decreased PAR-2 mRNA expression in BEAS-2B cells by 20% after 24 h (n=12, independent T-test p< 0.001). IL-4 (20 µg/ml) showed a similar trend, but the inhibitory effect was not statistically significant (n=3). Several other inflammatory stimuli (lipopolysaccharide, cockroach and house dust mite extracts, and PAR-2 activating peptides) had no effect on PAR-2 expression, however sample sizes were low in all cases (n=2 or 3).

Conclusions: Decreased PAR-2 expression following activation of airway ECs with IL-13 may indicate a negative feedback loop in the airways; PAR-2 activation promotes allergic inflammation, but cytokines present during allergic inflammation decrease PAR-2 expression to limit adverse effects of allergic inflammation. Understanding regulation of PAR-2 expression in the airways may lead to identification of new approaches to treat allergic inflammation.
Outcomes of Indwelling Pleural Catheters in Malignant Pleural Effusions: Do Patients who are Followed in a Specialized Pleural Effusion Clinic Have Better Outcomes?

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Introduction: Malignant pleural effusions (MPE) are a common cause of refractory pleural effusions. The presence of an MPE often signifies metastatic disease and portends to a poor prognosis, with a median survival of 3 months. The focus of management is palliative in nature with emphasis on improving the patient’s quality of life. Placement of indwelling pleural catheters (IPCs) under ultrasound-guidance is the standard management of MPEs. IPCs are tunneled pleural catheters that can be inserted in an outpatient clinic setting and can be drained with homecare support for symptomatic relief. Complications are low but include infection such as localized cellulitis or empyema.

A multidisciplinary specialized Pleural Effusion Clinic (PEC) has been developed in Edmonton to see these patients in consultation and for ongoing management. In some clinical settings, IPCs are inserted by Interventional Radiology (IR) as a “one-time procedure”, and with no specialized follow-up. To our knowledge, there is no literature available on outcomes for these patients. As such, our study aims to evaluate the outcomes of patients followed in our specialized Pleural Effusion Clinic in comparison to those that are not.

Methods: A retrospective chart review was conducted on a cohort of patients over the age of 18, living in Alberta, who had an IPC inserted between 1 February 2014 and 31 October 2015 in the PEC or by IR. General characteristics and occurrences of complications were recorded. Outcomes measured include repeat chest procedures, infection (cellulitis and empyema), number of hospital visits, and others.

Results: When comparing patients from the PEC group (n=96) to the IR group (n=49), there was a higher rate of repeat chest procedures, infection, hospital visits in the patient cohort who did not receive specialized follow up (53% versus 32.3%, p=0.015). Patients who had IPCs inserted by IR had a higher rate of IPC reinsertion of 18.4% as compared to 6.3% in the PEC group (p=0.023).

Conclusion: In conclusion, this study suggests that there is benefit for patients with IPCs to receive specialized follow-up care. Future work includes studying a larger cohort of patients over a longer period to confirm these preliminary results.
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