

Alberta Respiratory Centre ARC Research Day 2020

Wednesday, November 18, 2020

11:00 am – 2:30 pm

Virtual (Zoom)

Edmonton, AB

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Message from Director of ARC Research

Dear Colleagues,

I would like to extend a warm welcome all of you to our 12th 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 **24** 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.

This year we have had to move our Research Day to a virtual platform due to the pandemic, and we are pleased to have BUKSA helping us host this event online. All participants will be asked to participate through Zoom meetings, which we hope will be a familiar platform for interactions for everyone. Special thanks go to Anita Kozyrskyj, the Co-Director of ARC Research, the ARC Research Committee (Richard Long, David Marchant, Joanna McLean, Maria Ospina, and Subhabrata Moitra) and Colette Breedevelt for helping to coordinate this event.

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 attend 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.

The 23rd **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 be honoured in years to come. We are delighted to have Dr. Leonardo Fabbri from the University of Ferrara in Italy, as this year's distinguished Brian J. Sproule lecturer. Dr. Fabbri's virtual presentation will initiate ARC Research Day from 11 a.m. to 12 p.m.

I would also like to thank our sponsors, AstraZeneca, GSK, the Alberta Health Services Medicine Strategic Clinical Network, Sanofi Genzyme, and Boehringer Ingelheim (Canada) Ltd., for providing their valuable support to make this a successful event. I hope to see you all at the Brian J. Sproule Lectureship and during the poster session.

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

Program

| Time | Program |
|----------------------|---------------|
| 11:00 am to 12:00 pm | Lecture |
| 12:00 pm to 2:00 pm | Poster Q & A |
| 12:00 pm to 2:00 pm | Lunch |
| 2:00 pm to 2:30 pm | Poster Awards |

Adjudication Committee

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

Dr. Mohit Bhutani, Professor, Pulmonary Medicine

Dr. Maria Castro-Codesal, Associate Professor, Pediatrics

Dr. Alim Hirji, Assistant Professor, Pulmonary Medicine

Dr. Anita Kozyrskyj, Professor, Pediatrics

Dr. Grace Lam, Assistant Professor, Pulmonary Medicine

Dr. Cheryl Laratta, Assistant Professor, Medicine

Dr. Richard Long, Professor, Pulmonary Medicine

Dr. Joanna MacLean, Associate Professor, Pediatrics

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

Dr. Maria Ospina, Assistant Professor, Obstetrics & Gynecology and Medicine

Dr. Lakshmi Puttagunta, Professor, Laboratory Medicine and Pathology

Dr. Dilini Vethanayagam, Professor, Pulmonary Medicine

Dr. Hari Vliagoftis, Professor, Pulmonary Medicine

Brian J. Sproule Lectureship

 UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Alberta Respiratory Centre (ARC)

ARC *Virtual* RESEARCH DAY

Wednesday, November 18, 2020

11:00 am – 12:00 pm

Brian J. Sproule Lectureship

Guest Speaker, Dr. Leonardo Fabbri

“COPD as Pulmonary Component of Chronic Multimorbidity”

12:00 - 2:30 pm

Poster Sessions and Awards

*Sponsored by AstraZeneca, GlaxoSmithKline,
Boehringer Ingelheim, Sanofi Genzyme and
Respiratory Section - Medicine Strategic Clinical Network*



A new Division of Pulmonary Medicine online attendance sign-in system has been implemented which has replaced the former sign-in sheets. Scan this QR code to take you to the new system or go to website https://rounds.med.ualberta.ca/log_in

“uplifting the whole people”

— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908

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Progressive Dyspnea with Recurrent Pneumothoraces

Jake Mandziuk, Kai L. Homer, Alim Hirji, James Barrie, Steven R. Meyer, Eric Y.L. Wong, Lakshmi Puttagunta, Kieran Halloran

Department of Laboratory Medicine and Pathology

Introduction: Pleuroparenchymal fibroelastosis (PPFE) is a rare idiopathic interstitial pneumonia. It is a progressive condition in 60% of patients. Complications of PPFE include recurrent pneumothoraces and pneumonias. The condition has a 5-year survival rate of 30%. At this time, lung transplantation is the only definitive therapeutic intervention. In the literature, the pathologic changes of PPFE are reported to involve the upper lobes only. Herein, we present a case of confirmed PPFE showing central lung and lower lobe involvement.

Case Presentation: A 34-year-old male presented with dyspnea, cough, and chest tightness. He was diagnosed with a pneumothorax and admitted for high-flow oxygen therapy. Computed tomography of the chest showed upper-lobe predominant pleuroparenchymal thickening, bilateral perilymphatic nodularity, bilateral lower lobe peribronchial nodules, and tracheobronchomegaly. After discharge, he deteriorated clinically and was readmitted six times, over a period of thirteen months, with recurrent pneumothoraces treated with pigtail catheter placement. During his seventh admission, he required mechanical thoracoscopic pleurodesis for refractory pneumothorax. Postoperatively, he became hypoxemic and was reintubated, ventilated, and eventually placed on veno-venous extracorporeal membrane oxygenation. He ultimately underwent bilateral orthotopic sequential lung transplantation. Pathological assessment showed bilateral dense pleural fibrosis, subpleural parenchymal fibroelastosis, and extension along fissure lines to encase central airways and pulmonary vasculature, predominantly in the upper lobes, with notable lower lobe involvement. On the basis of clinical, radiologic, and pathologic evidence, a diagnosis of PPFE was made.

Discussion: The characteristic clinical presentation of PPFE is progressive dyspnea associated with cough, weight loss, and pleuritic chest pain. PPFE may be idiopathic, however is also associated with hematopoietic stem cell and lung transplantation, pulmonary infections, chemotherapy, autoimmune diseases, chronic hypersensitivity pneumonitis, and exposures to asbestos or aluminum. There are proposed radiographic and histopathologic criteria for the diagnosis of PPFE; however, upper lobe involvement with minimal lower lobe involvement is classically described. Herein, we present a case of PPFE in a young patient with extensive lower lobe involvement.

Conclusion: PPFE is a rare pulmonary interstitial pneumonia that can follow a fulminant course leading to respiratory failure. It is important to recognize PPFE at an early stage such that patients with evidence of progression may be evaluated for lung transplantation with no unnecessary delay, particularly in young individuals. Our case demonstrates that extension of characteristic changes of PPFE beyond the upper lobes should not exclude a diagnosis of PPFE. Thus, current diagnostic criteria which state that lower lobe involvement precludes PPFE should be revisited.

Pre-transplant Malignancy is Associated with Increased Post-transplant Malignancy Risk in Lung Transplant Recipients

Viktor Sekowski, Kathy Jackson, Kieran Halloran, Rhea Varughese, Justin Weinkauff, Ali Kapasi, Dale Lien, Alim Hirji

Department of Medicine, University of Alberta, Edmonton, Canada

Introduction: At least one in five lung transplant recipients will be diagnosed with a posttransplant malignancy (PostTM) within 5 years of transplant. Immunosuppression is associated with an increased incidence of cancer occurrence, with potentially higher risk in those that have already developed malignancy before transplant. As a center that adheres to international guidelines regarding listing and pre-transplant malignancy (PreTM), we assessed whether PreTM was associated with increased risk of developing a malignancy after lung transplant.

Methods: We conducted a single centre retrospective cohort study of patients undergoing lung transplant between January 2006 and December 2017, identifying patients with a history of PreTM and patients who developed PostTM (solid organ, cutaneous, post-transplant lymphoproliferative disorder [PTLD] and leukemia). We performed a univariate Cox regression to assess for potential risk factors for post-transplant malignancy in our cohort. We then used a Cox proportional hazards model to assess whether PreTM was associated with the risk of developing one or more PostTM after lung transplant, adjusted for malignancy risk factors including age at transplant, sex, diagnosis, body mass index (BMI), smoking history >20 pack years and induction type.

Results: 514 adult patients underwent lung transplantation during the study period. 29 patients had a PreTM history. 110 patients developed PostTM with a total of 331 cancer diagnoses; 283/331 (85.5%) were non-melanoma cutaneous malignancy and 28 were solid organ malignancies. For patients with a PreTM history, the median time between their PreTM and transplant was 4.5 years. Recurrences of the PreTM occurred in 4 patients post-transplant. Our univariate analysis found that older age at transplant, male sex, higher BMI, COPD/alpha-1 anti-trypsin and ILD diagnoses were associated with higher PostTM risk. PreTM history was associated with an adjusted HR of 3.19 (95% CI 1.72 to 5.94, $p < 0.001$) for the development of a PostTM. Excluding PTLT and leukemia, the HR increased to 3.77 (95% CI 2.00 to 7.09, $p < 0.001$) for patients who developed PostTM.

Conclusions: Lung transplant patients with a PreTM were more than three times more likely to develop a PostTM than patients without a history of malignancy in our cohort; the majority of PostTMs were unrelated to the initial PreTM. This elevated risk highlights the importance of frequent cancer surveillance of this post-lung transplant cohort.

Clinical Characteristics of Noninvasive Positive Pressure Ventilation Use in Canadian Patients with Cystic Fibrosis

Sophie Walton, Dr. Winnie Leung, Dr. Anne Stephenson, Dr. Emad Saad
Presenting Author: Dr. Sophie Walton, Internal Medicine PGY3

Institutional Affiliation of Presenting Author: University of Alberta, Edmonton, Alberta

Introduction: Pulmonary disease remains the most frequent cause of morbidity and mortality among patients with cystic fibrosis (CF). Noninvasive positive airway pressure ventilation (NPPV) has been shown to stabilize lung function and improve outcomes in end-stage CF lung disease. This study aims to characterize the use of NPPV in Canadian patients living with CF and to identify patient factors that are associated with NPPV use.

Methods: Data from the Canadian Cystic Fibrosis Registry was used to identify adult patients (>18 years old) as of January 1st, 2011. The Registry contains clinical data submitted from 42 CF clinics across the country. Patients with severe disease were included if they had at least one pCO₂ > 45mmHg and one FEV₁ % predicted < 40% between 2011-2018. Patients were categorized into two groups based on whether or not they received NPPV in the study period. Patients who received a lung transplant prior to NPPV use were excluded. Categorical variables were compared using Chi-square or Fisher's test while continuous variables were compared using independent T-test or Wilcoxon rank sum test. The FEV₁ analysis was done using a robust linear mixed effect model. Approval was obtained from the University of Alberta Health Research Ethics Board.

Results: A total of 219 patients were included in the study. 32.8% (n=72) of patients used NPPV at least once between 2011-2018. Age at time of first NPPV use was 34.5 +/- 11.6 years and the FEV₁ % predicted was 29.2% +/- 12.9. FEV₁ % predicted was found to be 7.27% +/- 2.46 lower in the NPPV group when compared to the non-NPPV group (p=0.0031). Prevalence of *Stenotrophomonas maltophilia* (p=0.0045), and *Aspergillus* (p=0.0448) were higher in NPPV group while rates of *Pseudomonas aeruginosa*, (p=0.0389) were higher in the non-NPPV group. The NPPV group had higher rates of feeding tube insertions (p<0.0001), more commonly required home oxygen (p=0.0005) and were more likely to receive a lung transplantation (p=0.0001). No difference was identified between the NPPV and non-NPPV group in need for home IV antibiotics or hospitalizations.

Conclusions: Over 30% of Canadian CF patients with end-stage lung disease received NPPV during the study period. NPPV use in CF is associated with lower lung function, need for nutritional supplementation and lung transplant. Additional research is needed to understand the impact of NPPV on lung function decline and which subgroup of patients are most likely to benefit from this intervention.

High Immunologic Risk Lung Transplantation Using Risk Stratified Induction

Melissa Wang MD, Patricia Campbell MD, Esme Dijke PhD, Dale Lien MD, Rhea Varughese MD, Justin Weinkauff MD, Ali Kapasi MD, Jayan Nagendran MD PhD, Alim Hirji MD MSc, David Li BSc, Kieran Halloran MD MSc

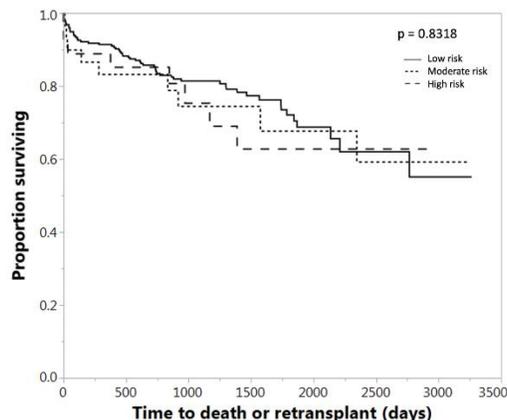
Department of Medicine, University of Alberta, Edmonton, Canada

Introduction: Donor specific antibodies (DSA) are associated with antibody-mediated rejection, chronic lung allograft dysfunction (CLAD) and increased mortality, making lung transplant in the presence of DSA high risk. Our center transplants these patients using risk-stratified induction. We sought to assess survival and time to CLAD onset in these patients compared to low risk recipients.

Methods: We reviewed lung transplant recipients transplanted from January 2010 to December 2017. Recipients were assigned to three risk categories: low [no DSA, negative crossmatch (XM)], moderate [positive DSA, negative XM] and high [positive DSA, positive XM]. Patients with DSA were treated with anti-thymocyte globulin and intravenous immune globulin, with five cycles of pheresis for positive XM. Low risk patients received basiliximab. We used Cox regression to test the association between risk category and time to death or retransplant as well as time to CLAD onset, and logistic regression to test the relationship between risk category and severe primary graft dysfunction (PGD).

Results: 313 patients met inclusion criteria and 76 died during follow up. 256 (81%) were low risk, 27 (9%) moderate and 30 (10%) high. Patients with pre-transplant DSA were younger and more likely to be bridged to transplant. There was no effect of risk status on survival either unadjusted (Figure 1, $p=0.83$) or adjusted for age, diagnosis, bridging status and transplant type ($p=0.65$). There was no relationship to time to CLAD onset ($p=0.61$). Patients with DSA were at increased risk of severe PGD, both unadjusted ($p=0.002$) and adjusted for age, diagnosis and bridging status ($p=0.01$), mainly high vs. low risk (adjusted odds ratio 0.29, [95% CI 0.12-0.70]).

Conclusions: Using a risk stratified induction strategy, DSA at time of transplant was not associated with increased risk of death or CLAD onset in lung transplant recipients, suggesting this is a safe way to improve access for sensitized recipients. The novel PGD association warrants further investigation.



Early Breastfeeding is Associated with Reduced Gut Microbiota Abundance of Christensenellaceae at One Year of Age; No Protection Against Preschool Asthma

Yuan Y. Chen, Hein M. Tun, Meghan B. Azad, Allan B. Becker, Piush J. Mandhane, Theo J. Moraes, Malcolm R. Sears, Stuart E. Turvey, Padmaja Subbarao, James A. Scott, Anita L. Kozyrskyj

3-527 Edmonton Clinic Health Academy, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Introduction: The protective effects of breastfeeding against asthma development are inconsistent. When administered as a probiotic, *Bifidobacterium* has been found to reduce respiratory symptoms in children with milk allergy; after 6 months of probiotic treatment, Christensenellaceae were reportedly depleted in gut microbiota. Indeed, a higher abundance of this heritable family in gut microbiota at age 3 years was found to be cross-sectionally associated with asthma in another study. The role of Christensenellaceae in breastfeeding associations with asthma is unknown. Therefore, the present study aims to determine whether breastfeeding influences Christensenellaceae abundance in infant gut microbiota and whether this association impacts the development of preschool asthma.

Methods: This study included 1,958 term infants representing a subset of CHILD birth cohort. Maternal self-report was used to determine feeding method (exclusive, partial and not breastfeeding) in the first 3 months of age, infant sex and maternal race. Children were clinically assessed for a diagnosis of asthma at age 5 years. 16S rRNA gene sequencing was performed to profile the abundance of Christensenellaceae in infant fecal samples that were collected at one year of age. The impact of breastfeeding on the abundance of Christensenellaceae was evaluated using linear regression, adjusted for sex and maternal race. Logistic regression modelling, adjusted for the same factors, was pursued to test associations between breastfeeding status or Christensenellaceae abundance, and asthma at age 5.

Results: In our cohort, Christensenellaceae was detected in 8.2% (n=161) of infants at one year of age. Compared to infants who were not breastfed at 3 months, the abundance of Christensenellaceae at age 1 year was significantly decreased in exclusively breastfed infants (adjusted $\beta = -0.28$, 95% Confidence Interval [CI] = -0.47 to -0.09; $p = 0.004$) and tended to be reduced by partial breastfeeding ($\beta = -0.21$, CI = -0.42 to 0.01). However, there was no significant association between breastfeeding status or the abundance of Christensenellaceae, and preschool asthma at age 5.

Conclusions: Our findings show an inverse association between breastfeeding status and gut abundance of the family Christensenellaceae, which was not translated into reduced risk for preschool asthma.

Short-term Acute Exposure to Wildfire Smoke in Association with Lung Function in a First Responder Royal Canadian Mounted Police (RCMP) Cohort

Subhabrata Moitra, Ali Farshchi Tabrizi, Dina Fathy, Samineh Kamravaei, Kawtar Idrissi Machichi, Noushin Miandashti, Linda Henderson, Fadi Khadour, Muhammad T. Naseem, Lyle Melenka, Paige Lacy

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

Introduction: The increasing occurrence of extreme wildfires is becoming a major concern for public health due to high levels of particulate matter and toxic materials emanating from smoke. Although long-term exposure to wildfire smoke has been associated with respiratory illnesses (e.g., in firefighters), reports on the association between short-term acute exposures to wildfire smoke and lung function remain scanty.

Methods: In this cross-sectional study, we analyzed data from 218 RCMP officers (mean age: 38±9 years) who were deployed at the Fort McMurray wildfires in 2016 and were screened at Synergy Respiratory Care, Sherwood Park, AB. Demographic profiles and family histories were obtained using a structured questionnaire. Lung function was measured using spirometry and body plethysmography. Individual exposure to air pollutants was calculated by combining the duration of deployment with air quality parameters obtained from the nearest air quality monitoring station. Exposure to all pollutants were combined using principal components analysis (PCA). The association between the exposure and lung function was examined by linear regression, adjusting for potential confounders. Potential effect modification by smoking, any airway obstruction, childhood smoke exposure, and parental lung disease were also tested.

Results: Participants were mostly male (71%) and the median (range) duration between their deployment and the visit to the clinic was 60 (33-627) days. The mean forced expiratory volume in 1 second (FEV₁, % predicted), residual volume (RV, % predicted), total lung capacity (TLC, % predicted), and their ratio (RV/TLC) were 96.2±12.4, 80.1±19.5, 95.3±11.1, and 22.4±4.8, respectively. In PCA, one air pollution component was derived explaining a total of 88% of the variance. In multivariate analysis, air pollution was found to be marginally associated with higher RV [regression coefficient (β): 1.55; 95% confidence interval (CI): -0.28 to 3.37], and RV/TLC [β: 0.28; 95%CI: -0.12 to 0.67]. A stronger association was observed in participants who were screened within the first three months of deployment, indicating an acute effect of exposure to wildfire smoke-associated pollution on peripheral airways. We did not observe any effect modification by the presence of other potential influencing factors.

Conclusions: Although short-term acute exposure to wildfire smoke-related air pollutants were not associated with significant spirometric lung function indices, marginal associations with body plethysmographic indices indicate more deleterious effects of wildfire smoke exposure on peripheral airways. Therefore, more sensitive measurements of peripheral airways would be potentially helpful in diagnosing long-term respiratory health effects due to short-term acute exposure to air pollutants.

Infant Vitamin D Supplementation is Linked to Fecal Metabolites, Glycerol and 1,2-propanediol: Potential Implications for Lung Health

Authors: Xin Zhao, Kelsea M Drall, Sarah Bridgman, Mandal Rupasri, Meghan B Azad, Allan B Becker, Piush J Mandhane, Theo J Moraes, Malcolm R Sears, Stuart E Turvey, Padmaja Subbarao, James A Scott, Anita L Kozyrskyj

Department of Pediatrics, University of Alberta, Edmonton Clinic Health Academy (ECHA) building 11405-87 Avenue, Edmonton, AB, Canada

Introduction: Infant vitamin D liquid formulations often contain stabilizers, glycerol or 1,2-propanediol (1,2-POD), which are available to gut microbiota due to poor absorption in the colon. Our previous study suggests infant vitamin D supplementation correlates with gut microbes, *Megamonas* spp. potentially involved in asthma or viral respiratory infections. Experiments demonstrate that acetate and propionate may prevent allergic asthma. However, nothing is known about the impact of routine vitamin D supplementation of breastfed infants on the intestinal levels of these stabilizers. The primary aim of this study was to investigate the effects of vitamin D supplementation on fecal levels of glycerol and 1,2-POD, and the correlation of these stabilizers with gut microbes and metabolites relevant to lung health.

Methods: Fecal samples and vitamin D supplementation and breastfeeding status information were obtained at 3-month age for 575 infants from the Canadian Healthy Infant Longitudinal Development (CHILD) Study. Fecal metabolites and microbiota were quantified using Nuclear Magnetic Resonance Spectroscopy and 16S rRNA sequencing, respectively. Linear and logistic regression were used to determine the association between vitamin D supplementation with fecal concentrations of glycerol and 1,2-POD, adjusting for covariates. Spearman rho was computed to evaluate correlations between taxa and metabolites with the fecal glycerol and 1,2-POD.

Results: Seventy eight percent of the exclusively breastfed infants were supplemented with vitamin D drops (containing glycerol). High fecal 1,2-POD concentrations (above the median) were much more common in infants compared to those without vitamin D supplementation (61.2% vs. 34%, $p < 0.001$). Independent of breastfeeding status and infant ages, vitamin D supplementation was associated with 1.6-fold odds of high 1,2-POD (adjusted-OR=1.58, $p < 0.05$), and 41% reduced odds of high fecal glycerol (adjusted-OR=0.59, $p < 0.05$). Fecal 1,2-POD was positively correlated with proportions of *Lactobacillus* spp. ($p < 0.05$), Enterobacteriaceae ($p < 0.05$), *Haemophilus* spp. ($p < 0.05$), and *Bifidobacterium* spp. ($p < 0.05$), whereas negatively correlated with *Akkermansia* ($p < 0.05$), Veillonellaceae ($p < 0.05$) and Lachnospiraceae ($p < 0.05$). Accordingly, fecal acetate ($p < 0.05$) and lactate ($p < 0.05$) were positively correlated with 1,2-POD, whereas butyrate ($p < 0.05$) and propionate ($p < 0.05$) were negatively correlated with fecal 1,2-POD.

Conclusions: Infants supplemented with vitamin D exhibit higher levels of fecal 1,2-POD. Certain microbiota, notably bifidobacteria, metabolize glycerol to 1,2-POD. This link with probiotic microbiota and observed 1,2-POD associations with microbial acetate and propionate levels have implications for lung health. This study brings awareness to non-medicinal ingredients in infant vitamin D supplements and their potential implications in infant health.

German Cockroach Extract Proteolytic Activity Inactivate Interleukin-13 (IL-13) and Down-regulate IL-13-induced CCL26 in Airway Epithelial Cells

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Introduction: Airway epithelium activation by inhaled allergens is a key trigger of allergic immune responses. Exposure to cockroach allergens in U.S. inner-city communities is a major risk factor for asthma morbidity. Cockroach allergens have been identified to possess protease activity, mostly serine protease activity. In some studies CE proteases were connected to the activation of Proteinase-Activated Receptor-2 (PAR-2) which is a major trigger of inflammation. IL-13 is a Th2 mediator believed to be central in the development of allergic asthma and known to induce epithelium Eotaxin-3 (CCL26) production. CCL26 is the most effective chemoattractant to induce eosinophil migration and the highest expressed eotaxin in human cultured airway epithelial cells. This work aimed to understand the interactions of CE proteases with IL-13 in airway epithelial cells and PAR-2 activation.

Methods: BEAS-2B, a virus transformed bronchial epithelial cell line, and normal human bronchial epithelial (NHBE) cells were cultured in pre-coated multi-well plates until 90% confluent. Cells were then growth factors deprived for 24 hours prior to activation. Cells were stimulated with IL-13, CE or both. CCL26 mRNA was measured by RT-PCR and CCL26 protein by ELISA. To investigate the role of CE proteases, heat inactivated CE (HICE) or CE pre-incubated with aprotinin (serine), E64 (cysteine), or pepstatin (acid) protease inhibitors were used. Cells were also activated with PAR-2 activated or control peptides (AP) (CP). Flow cytometry were used to measure expression of IL-13R α 1 on cell surface. Western blotting used to assess IL-13 protein cleavage.

Results: IL-13-induced CCL26 mRNA expression and protein release in bronchial epithelium BEAS-2B and primary cells. CE down-regulated IL-13-induced CCL26 mRNA and protein in PAR-2 independent manner. HICE and CE pre-incubated with aprotinin, a serine protease inhibitor, did not inhibit IL-13-induced CCL26. CE did not change the expression of IL-13R α 1 but inhibited IL-13R α 2 mRNA expression. Western blot showed cleavage of IL-13 protein by CE proteases. IL-13 protein cleavage was not inhibited when CE was pre-incubated with serine or, cysteine protease inhibitors or with HICE.

Conclusions: CE down-regulates IL-13-induced CCL26 mRNA and protein release in airway epithelial cells and cleave IL-13 protein in solution. IL-13 cleavage by CE serine proteases may inactivate IL-13 and down-regulate IL-13-induced CCL26. However, IL-13 cleavage by CE proteases, other than serine, could not alter IL-13 activity. This data suggest that inhaled CE serine proteases may alter the biological activity of IL-13 including IL-13-induced CCL26 and the subsequent eosinophilic migration in a PAR-2 independent manner.

The Effect of Inhaled Nitric Oxide on Exercise Capacity in Chronic Obstructive Pulmonary Disease

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Introduction: Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive, partially reversible airway obstruction, dyspnea and exercise intolerance. Dyspnea in COPD patients is partly explained by an exaggerated ventilatory response to exercise [determined by the ventilatory equivalent for carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$)]. The increased $\dot{V}_E/\dot{V}CO_2$ in mild COPD can be explained by pulmonary vascular dysfunction resulting in ventilation-perfusion abnormalities, specifically, areas of normal ventilation but low relative perfusion (i.e. deadspace ventilation). Our prior work has shown that inhaled nitric oxide (iNO) improves ventilation and exercise tolerance and reduces dyspnea by modifying pulmonary vascular function in mild COPD. In advanced COPD, there is progressive pulmonary vascular destruction, making it unclear whether vascular dysfunction represents a therapeutic target. The purpose of this study is to determine the effect of iNO on $\dot{V}_E/\dot{V}CO_2$, dyspnea and exercise capacity in patients with moderate and severe COPD. We hypothesize iNO will improve exercise capacity in moderate COPD, secondary to a reduction in $\dot{V}_E/\dot{V}CO_2$, while no effect will be observed in severe COPD.

Methods: In a randomized placebo-controlled double-blind cross-over study, patients with moderate COPD were recruited. Patients with heart failure, pulmonary hypertension, or those taking pulmonary vascular medication were excluded. **Protocol:** **Day 1:** Enrollment, medical history, pulmonary function test, and a symptom limited incremental (20 Watt·2 min⁻¹) cardiopulmonary exercise test (CPET) to determine peak oxygen consumption ($\dot{V}O_{2peak}$). **Days 2/3:** CPET breathing room air (placebo, 21% O₂, 79% N₂) or iNO (room air with 40ppm iNO; randomized). $\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ were recorded continuously, and dyspnea ratings were obtained every 2min.

Results: Data are presented as mean±SEM. In the patients tested to date (4 males, 2 females; Age: 72.5±0.2 years; BMI: 24.0±0.6kg/m²; forced expiratory volume in 1sec (FEV₁): 66.2±2.9%_{pred}), there was no change in $\dot{V}O_{2peak}$ with iNO (placebo: 1.53±0.17 vs iNO: 1.56±0.23 L/min, p=0.69). iNO did not have a significant effect on $\dot{V}_E/\dot{V}CO_2$ (placebo: 30.7±1.0 vs iNO: 32.3±0.8, p=0.11) or dyspnea (placebo: 6.0±0.7 vs iNO: 5.7±1.1, p=0.74) at peak exercise.

Conclusion: Initial results suggest that iNO does not improve exercise capacity, $\dot{V}_E/\dot{V}CO_2$, or dyspnea in patients with moderate COPD, which is in contrast to our earlier work in patients with mild COPD. Our findings would suggest that patients with moderate COPD exhibit signs of vascular destruction. This study will help identify COPD patients with pulmonary vascular dysfunction that are responsive to iNO and help identify the clinical phenotype which may be responsive to pulmonary vascular therapy.

Cytokine Production in Allergen-stimulated Airway Epithelial Cells Shows Time-dependent Increases in Intracellular Thymic Stromal Lymphopoietin

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Introduction: Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness and bronchoconstriction in response to exercise or allergens in atopic individual. The airway epithelium lining the lungs releases pro-inflammatory cytokines capable of inducing an immune response after sensing its environment through different receptor types. However, few studies have examined intracellular cytokine movement in allergen-stimulated airway epithelial cells. We aim to study intracellular trafficking mechanisms utilized by airway epithelial cells to release cytokines after activation of their receptors. We hypothesize that airway epithelial cell activation by allergens induces intracellular production of pro-inflammatory cytokines through vesicular trafficking mechanisms.

Methods: To serve as a model of airway epithelial cell activation and cytokine production, we established a cell culture of an airway epithelial cell line, BEAS-2B cells. BEAS-2B cells were grown in 24-well plates on glass coverslips until they reached 70-80% confluency. Cells were then stimulated with cockroach extract (CE) or house dust mite (HDM) extract (5 $\mu\text{g}/\text{mL}$) over time (0 h, 4 h, 8 h, and 24 h). After stimulation, BEAS-2B cells were washed, fixed, and immunolabeled with primary antibodies to a panel of cytokines, which were detected by secondary antibodies conjugated to fluorescent dyes. Counterstaining of cells was carried out using rhodamine phalloidin to detect cytoskeleton and Hoechst to detect nuclei. Immunolabeled coverslips were imaged with an Olympus epifluorescence microscope, and image quantification analysis was performed using Volocity software, allowing analysis of arbitrary fluorescent intensities within cells delimited by cytoskeletal staining.

Results: In unstimulated cells (0 h), baseline expression of intracellular IL-1 β , IL-25 and TSLP could be detected relative to isotype controls. After 8 h of CE stimulation, intracellular levels of IL-1 β and IL-25 decreased ($p < 0.01$). Conversely, TSLP increased in a time-dependent manner levels following CE and HDM extract stimulation, with significant differences between 0 h, 8 h and 24 h ($p < 0.01$). These observations were collected from at least two separate experiments for each allergen stimulation.

Conclusions: Our findings show that BEAS-2B cells have detectable increases in intracellular TSLP levels, concurrently with decreased IL-1 β and IL-25, in response to direct allergen stimulation. Such differential intracellular cytokine responses to allergen have not been reported in epithelial cells. We aim to reproduce these experiments in primary human airway epithelial cell. These observations will contribute to our understanding of intracellular cytokine production in airway epithelial cells, and provide mechanistic insights into their trafficking and release.

Evaluating the Influence of Variance in Pulmonary Rehabilitation Programs on Health Outcomes

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Introduction: Pulmonary rehabilitation (PR) is an effective therapy for patients with chronic respiratory diseases, but variability in program delivery may impact PR outcomes. The Canadian Standardized PR Program was developed to aid healthcare providers in delivering efficient, best-evidence PR. Complimentary to this program are the Canadian Thoracic Society quality indicators (QI) for PR, designed to identify program variation, and improve health outcomes. The roll-out of the Canadian Standardized PR Program through the Breathe Easy Program (BEP) to 33 sites across Alberta provided an opportunity to a) examine how each site varied in delivery of BEP program components and QIs, and b) evaluate the impact of this variation on accepted PR outcomes.

Method: Program alignment with the BEP was evaluated via a standardized survey. Evaluated domains included exercise programming, group education, individual education, and measures QIs. The survey was scored by clinician experts using a predetermined algorithm. The relationship between the program variance and changes in exercise tolerance (6MWD) and health-related quality of life (CAT) was examined using a cut-score for program alignment of 80% or higher. The difference between groups was evaluated using a t-test or one-way ANOVA.

Results: 19/33 (58%) of sites were assessed for program variance. Exercise programming alignment to BEP ranged from 71% to 97%, while the alignment with group education ranged from 81% to 93%. The alignment of the individual education component with BEP showed the greatest variance, ranging from 49% to 100%. There was no difference in change in 6MWD ($33 \text{ m} \pm 51 \text{ m}$ vs. $41 \text{ m} \pm 57 \text{ m}$, $p = 0.321$) or CAT (-2.5 ± 5.2 vs. -2.8 ± 6.0 , $p = 0.77$) between programs who met the 80% cut-off for individual education vs. those which did not.. Of the 14 quality indicators, 3 centres met 11, 7 met 12, and 7 met 13 quality indicators. There were no differences in change in 6MWD ($13 \pm 64 \text{ m}$ vs. $31 \pm 61 \text{ m}$ vs. $35 \pm 52 \text{ m}$, $p = 0.321$) and CAT (-1.25 ± 3.9 vs. -3.6 ± 6.6 vs. -2.52 ± 5.2 , $p = 0.317$) between sites that met 11 vs. 12 vs. 13 quality indicators.

Conclusions: Overall, there is limited variance in the provincial roll-out of the BEP across 19 sites in Alberta, and sites typically achieved most of the national quality indicators. Importantly, initial results suggest that program variance does not appear to impact patient outcomes from PR.

Evaluating Health Outcomes from the Scale and Spread of the Breathe Easy Pulmonary Rehabilitation Program in Alberta

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Introduction: Pulmonary rehabilitation (PR) is an important but underutilized therapy for patients with respiratory diseases. National PR experts developed the Canadian Standardized Pulmonary Rehabilitation Program to aid health care providers in delivering efficient, best-evidence PR across a variety of clinical settings. Locally, this new program has been operationalized at the GF MacDonald Centre for Lung Health as Breathe Easy Pulmonary Rehabilitation (BEP). In 2018, BEP and partners within Alberta Health Services (AHS) aimed to spread and scale the program across all five health zones within AHS. This study aimed to compare outcomes in exercise tolerance and health-related quality of life among the different BEP sites to determine the effectiveness of the scale and spread.

Methods: A prospective, multicentre observational study of the scale and spread of BEP in Alberta. Baseline and clinical data were collected in a secure RedCap database between December 2018 and March 2020. Twenty-seven sites participated in this study, with a total of 1158 patients enrolled with various chronic respiratory conditions (average FEV₁ % predicted = 58 ± 24, Age = 68 ± 11 years, and BMI kg/m² = 29.6 ± 7.5). The primary outcomes were changes in the six-minute walk distance (6MWD) and COPD Assessment Test (CAT). Differences between sites were evaluated using a one-way ANOVA, with GF MacDonald Centre for Lung Health used as the index site.

Results: Four hundred and fifty-three patients at 13 sites had sufficient pre-post data for this analysis. Sample size at sites ranged from n=6 at two sites to n=310 at the index site. PR resulted in a significant improvement in both 6MWD and CAT (P<0.001). The average change in 6MWD was 34 ± 51m. Ten out of 13 sites (90% of patients) had a change in 6MWD above the MCID of 25 m. The ANOVA detected a significant difference across sites (p < 0.001), but no differences were observed compared to the index site. The average change in CAT was -2.6 ± 5.4. Eight of 13 sites (90% of patients) had a change in CAT score above the MCID of 2. There were no significant differences between sites (p=0.47).

Conclusions: The results would suggest that BEP can be spread across Alberta and that improvements in exercise tolerance and quality of life are similar across sites.

Cells Mediating PAR-2 Activation on 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). *Par-2*^{-/-} mice develop attenuated airway inflammation when compared to WT mice in mouse models of asthma. Furthermore, our lab demonstrated that, blocking PAR-2 activation in the airways, decreased allergic airway inflammation in mouse models of asthma, indicating that PAR-2 activation is essential for the development of allergic airway inflammation. However, the exact cell(s) activated by PAR-2 activating proteinases in the airways is not clearly understood. **We hypothesize that allergens possessing serine proteinases activity and/or endogenous proteinases, activate PAR-2 on airway epithelial cells leading to the release of pro-inflammatory mediators and allergic airway inflammation. Our aim is to identify the cell(s) promoting allergic airway inflammation following PAR-2-mediated activation.**

Methods: To understand whether the development of allergic airway inflammation requires PAR-2 expression on structural cells (among others airway epithelium) or hematopoietic cells we developed 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. To investigate if we can induce airway inflammation in *Par2*^{-/-} mice to the levels of WT mice we transferred CD4⁺ T cells from WT mice sensitized with house dust mite (HDM) to naïve *Par-2*^{-/-} mice and WT mice. After transfer of CD4⁺ T cells, the naïve *Par-2*^{-/-} and WT mice were challenged with HDM and airway inflammation was measured.

Results: Loss of PAR-2 expression on both structural and hematopoietic cells led to reduced allergic airway inflammation. However, there was significant reduction with the loss of PAR-2 expression on structural cells when compared to hematopoietic cells. Naïve *Par-2*^{-/-} mice injected with CD4⁺ T cells from spleens of HDM sensitized WT mice, developed allergic airway inflammation with a similar degree to WT mice after challenging with HDM.

Conclusions: Our results suggest that PAR-2 activation on structural cells, possibly airway epithelial cells, is critical for the development of allergic airway inflammation, however, PAR-2 activation on hematopoietic cells contributes to the development of the full effect. PAR-2 activation on structural cells, possibly airway epithelium induces the release of critical mediators essential for sensitizing lymphocytes which is missing in the case of *Par-2*^{-/-} mice. Interestingly, we can bypass this signal by transferring already sensitized lymphocytes to *Par-2*^{-/-} mice.

Systemic Corticosteroids and Lung Function Recovery after Respiratory Viral Infection in Lung Transplant Recipients

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Background: Respiratory viral infection (RVI) in lung transplant recipients (LTR) have variably been associated with poor outcomes. Our center uses systemic corticosteroids (orally or intravenous) in some RVI cases to treat inflammation based on clinical judgment, but evidence for this is limited.

Methods: We reviewed all adult LTR diagnosed with RVI (via nasopharyngeal swab or bronchoscopy) between 2017 and 2019. The primary outcome was recovery of lung function (forced expiratory volume in 1 second [FEV1]) at next stable visit between 1- and 12-months post-infection, expressed as a ratio between stable, representative FEV1 at follow up divided by stable FEV1 prior to infection (FEV1 recovery ratio). We modelled the association between steroid use and FEV1 recovery ratio using linear regression, adjusting for age, sex, transplant type, FEV1 presentation ratio (FEV1 at time of viral infection divided by stable FEV1 prior), hospitalization, coexistent bacterial or fungal infection, time post-transplant and CLAD status at infection.

Results: 158 patients were diagnosed with RVI, 62 (39%) of whom received corticosteroids. 9 patients (6%) died prior to any follow-up lung function, including two deaths attributed to infection and two to bronchiolitis obliterans. Baseline characteristics were similar between steroid treated and untreated, but steroid-treated patients had a lower FEV1 presentation ratio (0.90 vs. 1.00, $p=0.0094$) and were more likely to have CLAD at infection (26% vs. 10%, $p=0.0268$). Mean FEV1 recovery ratio was 1.00 (SD 0.20) with no relationship to specific virus type. Steroid treatment was not associated with FEV1 recovery ratio either unadjusted ($p=0.3709$) or adjusted ($p=0.4498$).

Conclusion: Treatment with systemic corticosteroids was not associated with improved FEV1 recovery in our cohort even after adjustment for presentation severity and other factors. This suggests systemic steroids have limited utility in the management of RVI in this population.

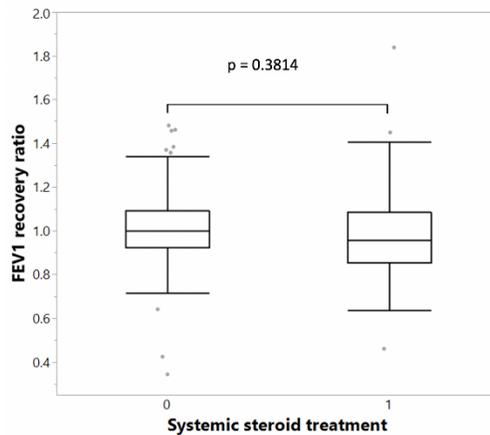


Figure 1. FEV1 recovery ratio stratified by the use of systemic steroids at time of infection. p-value reflects t-test.

Intracellular Cytokine Responses in Lung Epithelial Cells in Response to SARS-CoV-2 Infection

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Introduction: The airway epithelium plays an important role in defending the lungs from airborne contaminants and harmful pathogens. Infection of airway epithelial cells by SARS-CoV-2, the virus responsible for the current pandemic, has been shown to initiate a cytokine storm, in which a barrage of inflammatory cytokines is released that potentially overwhelm the immune system. However, there has been little evidence to show whether alarmin-type cytokines such as thymic stromal lymphopoietin (TSLP) are released in response to SARS-CoV-2. In this study, we analyze the cytokine response of lung epithelial cells in response to SARS-CoV-2.

Methods: Preliminary data was collected from NHBE, AHBE, Calu-3, and bronchial brushings. Bronchial brushings were collected from healthy individuals undergoing routine bronchial biopsy for unidentified lung masses. All cell types were grown in culture until they reached >80% confluency. Samples were then infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 1, for 24 hours. After infection, the cells were fixed using 4% paraformaldehyde and stained using a primary mouse anti-human TSLP antibody and a secondary antibody conjugated with Cy3. Cells were counterstained using Hoechst nuclear staining and a rhodamine phalloidin cytoskeletal stain. Images were collected using an Olympus IX81 fluorescent microscope and the mean intracellular fluorescence intensity was quantified using an automated algorithm on Volocity software.

Results: A significant increase in TSLP immunofluorescence ($p < 0.05$) was detected in NHBE ($n=3$) and AHBE ($n=3$) cells after 24 h infection with SARS-CoV-2 compared to isotype controls. In Calu-3 ($n=1$) cells, there was no significant increase in automated measurements of fluorescence intensity although cells appeared to visually show elevated TSLP fluorescence. At the time of writing, two bronchial brushings (AW01 and AW02) were collected. Bronchial brushings from AW01 showed a significant increase in immunofluorescence after 24 h infection, while bronchial brushings from AW02 did not show a significant increase in fluorescence after 24 h infection.

Conclusions: Infection of lung epithelial cells with SARS-CoV-2 was associated with a significant increase in TSLP immunofluorescence in airway epithelial cells, suggesting an increase in TSLP production. Therefore, lung epithelial cells can initiate immune signalling through the production and secretion of TSLP, and potential activation of nearby immune cells. Overexpression of pro-inflammatory cytokines during a SARS-CoV-2-induced cytokine storm may result in a disproportionate response to an infection, resulting in symptoms such as bronchoconstriction. Therefore, this study provides a framework to analyse and identify potential therapeutic targets for SARS-CoV-2 and other viral pulmonary infections.

An In Vitro Analysis of Continuous Flow Nitric Oxide Delivery via Nasal Cannula

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Introduction: Inhaled nitric oxide (NO) is currently used to treat mechanically ventilated patients in the critical care environment. Noninvasive delivery via nasal cannula has been investigated for patients with acute right ventricular dysfunction, with pulmonary arterial hypertension and with COVID-19. This study aims to determine the impact of breathing pattern, supply flow rate and nasal cannula type on inhaled NO concentration and mass flow for continuous flow NO delivery.

Methods: Carbon dioxide (CO₂) was used as a surrogate for NO, with 1% CO₂ representing 8 parts per million (ppm) NO. CO₂ and supplemental oxygen (O₂) were supplied through a nasal cannula to a realistic adult nose-throat airway replica. Soda lime was used to absorb CO₂, mimicking absolute NO uptake in the lungs. CO₂ flow rates, selected for a breathing pattern representative of COPD patient at rest, simulated targeted tracheal concentrations of 5 ppm NO (0.2 L/min CO₂ supply) or 20 ppm NO (0.8 L/min CO₂ supply) and were delivered concurrently with 2 L/min O₂. Patient breathing was generated using a servo-controlled lung simulator and breathing patterns were selected to represent rest, sleep and light exercise. These were later varied to further investigate the effects of tidal volume and breathing frequency changes. Three different cannulas were tested, two dual-lumen and one single-lumen. Measured tracheal CO₂ concentrations, along with CO₂ mass flow rate past the trachea, were converted to average inhaled NO concentrations and mass flow rates and are reported below.

Results: Cannula type had minimal effect on inhaled NO concentrations and mass flow rates. Inhaled tracheal NO concentrations changed significantly based on breathing pattern. For a target NO concentration of 20 ppm, average inhaled NO concentrations were 23.3 ± 0.5 ppm, 36.5 ± 1.4 ppm, and 17.2 ± 0.3 ppm, for the rest, sleep, and light exercise breathing patterns, respectively. For the same test conditions, mass flow rate of NO past the trachea was less sensitive to breathing patterns: 20.3 ± 0.5 mg/hr, 19.9 ± 0.8 mg/hr, and 24.3 ± 0.4 mg/hr for the rest, sleep, and light exercise patterns, respectively. Inhaled NO concentrations were predicted within ± 4.5 ppm using an assumption of complete mixing of the delivered NO within the inspired breath.

Conclusions: For continuous flow delivery, inhaled NO concentration is strongly influenced by breathing pattern, while inhaled NO mass flow rate is less sensitive to changes in breathing pattern. Prediction of inhaled NO concentrations and mass flow rates may help in establishing dose recommendations for noninvasive NO administration.

Computational Analysis of Calcium-binding Protein, Spermatid-associated 1 and Implications on its Biological Functions

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Introduction: It was previously reported that the heptapeptide TDIFEGG has anti-inflammatory effects in rats. This peptide is contained within a protein called Submandibular Rat 1 (SMR1). Humans do not have the SMR1 gene, so we conducted an analysis to find which protein in humans contained a similar sequence. We found that Calcium-binding protein, spermatid-associated 1 (CABS1) encodes the peptide TDIFELL and showed that it has anti-inflammatory activity *in vitro*. Interestingly, the genes encoding CABS1 in humans and SMR1 in rats are in a conserved cluster of genes across these two species, suggesting that SMR1's anti-inflammatory peptide was transferred to a different protein in humans, likely CABS1. We are now elucidating CABS1 function in humans. Our studies indicate that CABS1 is a marker of stress, that it is readily cleaved into discrete polypeptides, and that it is more widely distributed in human tissues than previously thought. Here we show the results of a hypothesis-generating computational analysis of CABS1.

Methods: Human CABS1 (hCABS1) sequence was used to generate 3D structural models using bioinformatic tools Raptor X, IonCom, and I-TASSER. The most reliable model was then used to test a library of potential hCABS1 ligands. Model validation was conducted using ProSA and ERRAT tools. We also used PONDR, FoldIndex, NetPhos to predict protein disordered regions and posttranslational modifications like phosphorylation and proteolytic processing. Phylogenetic analysis was conducted to investigate the evolutionary point at which the anti-inflammatory domain TDIFELL emerged within the CABS1 sequence.

Results: We obtained three predicted 3D molecular structures of hCABS1. The most reliable 3D model suggests that hCABS1 interacts with calcium, leucine, magnesium, zinc, and thiamine diphosphate (TPP) at specific co-factor binding sites. Moreover, hCABS1 is predicted to contain abundant disordered regions and can be phosphorylated at 8 serine residues. Interestingly, the anti-inflammatory domain TDIFELL is only observed in primates of the infraorder *Simiiformes*, which includes humans, and absent in other primates and non-primate species.

Conclusions: The abundance of disordered regions can explain why hCABS1 is readily cleaved into polypeptides. The flexible nature of these regions allows for exposure of domains that otherwise would remain hidden from proteases. We hypothesize that TDIFELL, conserved only in primates, is cleaved upon being exposed to proteases and has the anti-inflammatory activity similar to its isofunctional protein in rats, SMR1. Moreover, predicted binding to Ca^{2+} , Mg^{2+} , Zn^{2+} , Leu, and TPP, substrates of enzymes involved in energy metabolism, suggests that hCABS1 plays more roles than previously thought.

Lack of Change in Vascular Function Following a Mannitol Airway Challenge in Asthmatics

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Introduction: Asthma is a chronic airway disease characterized by recurrent episodes of airway inflammation leading to bronchoconstriction. Those diagnosed with asthma have a higher risk of developing cardiovascular disease, however the reasons for the increased risk are unknown and demand further investigation. It has been speculated that chronic airway inflammation in patients with asthma may cause vascular impairment and increased cardiovascular risk secondary to increased systemic inflammation. The novel bronchial challenge, Mannitol, induces airway inflammation and subsequent bronchoconstriction which may acutely lead to increased systemic inflammation and impaired vascular function in these patients. The purpose of the study was to determine if acute inflammation from a positive Mannitol inhalation challenge acutely reduces vascular function in individuals with asthma.

Methods: Twenty-four confirmed asthmatics completed a baseline pulmonary function test. On a separate day, baseline vascular function was assessed by % change in brachial artery diameter (% FMD), % FMD normalized to shear stress (AUC; % FMD/AUC), % FMD co-varied for AUC and velocity time integral (VTI). Arterial stiffness was assessed by carotid femoral pulse wave velocity (PWVCF) and carotid radial pulse wave velocity (PWVCR). Participants then completed a mannitol inhalation challenge. %FMD, % FMD/AUC, % FMD co-varied for AUC, VTI, PWVCF and PWVCR were evaluated within one hour of the challenge. Salbutamol was given to each participant before re-evaluation, regardless of the challenge outcome.

Results: Of the 24 asthmatics, 7 had a positive mannitol test (>10% reduction in FEV1 from baseline) and 17 had a negative mannitol test. There was a significant reduction in VTI ($p=0.014$) regardless of a positive or negative mannitol challenge, however, when normalized to heart rate there was no longer a significant decrease in VTI ($p=0.178$). There were no changes in arterial stiffness as measured by PWVCF ($p=0.392$) and PWVCR ($p=0.373$) or other markers of vascular function %FMD ($p=0.951$), % FMD/AUC ($p=0.615$) and %FMD co-varied for AUC ($p=0.620$) regardless of a positive mannitol challenge.

Conclusions: Contrary to our hypothesis, a positive Mannitol challenge in asthmatics did not acutely reduce systemic vascular function. The reduction in VTI following the mannitol challenge regardless of bronchoconstriction is consistent with our earlier work demonstrating reductions in vascular function with the administration of Salbutamol. Additional studies are needed to examine the chronic effects of Salbutamol on vascular function.

Comparing NIV Adherence in Children with Neuromuscular Disease Presenting Early or Advanced Stage Sleep Disordered Breathing

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Introduction: Children with neuromuscular diseases (NMDs) often develop sleep-disordered breathing (SDB) due to loss of upper airway muscle tone and weakness of respiratory muscles. Commonly, children with NMD initially develop SDB exclusively during Rapid Eye Movement (REM) sleep due to associated physiological muscle atonia. With disease progression, SDB affects both REM and non-REM sleep stages. While non-invasive ventilation (NIV) is the standard treatment for advanced SDB in children with NMDs, the use of NIV in earlier stages of SDB (REM-SDB) is less demonstrated and therapy adherence is unclear. This study aims to compare NIV adherence between children with early SDB (REM-SDB) and advanced SDB (NREM-SDB).

Methods: A dataset of children 0-18 years with a diagnosed NMD receiving NIV in Edmonton was used. An apnea-Hypopnea Index (AHI) ratio between REM and NREM sleep ≥ 2 was used to define the cases (REM-SDB). Conversely, an AHI ratio between REM and NREM sleep < 2 was used to define the controls (NREM-SDB). An independent sample t-test was used to determine differences in mean percentage of days with NIV use ≥ 4 hrs and mean nightly NIV hours in a 4-week period.

Results: Nine cases and 5 controls with 16 and 8 adherence reports, respectively, were included in the analysis. Case and control groups were homogenous in age, sex, underlying condition, cardiorespiratory parameters, and technology-related characteristics. There was a significant difference in the percentage of days with NIV usage ≥ 4 hours between cases ($69\% \pm 9.6$) and controls ($93\% \pm 2.7$). However, the average daily hours of NIV used was not significantly different between cases (9.2 ± 1.3) and controls (9 ± 0.4).

Conclusions: Children with REM-SDB and NREM-SDB both had high rates of NIV adherence, with no differences in mean nightly NIV hours. However, children with REM-SDB had lower days with sufficient NIV use (>4 hrs) suggesting less willingness to use the therapy compared with children with NREM-SDB.

Long-term Non-invasive Ventilation in Children with Down Syndrome: Exploring the Current State of the Evidence

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Introduction: Down syndrome confers susceptibility to multiple sleep-related breathing disorders, for which non-invasive ventilation (NIV) is a common treatment. While there is a large body of evidence for the use of long-term NIV in the broader pediatric population, work specific to its use in children with Down syndrome is more limited. Understanding the benefits and challenges of long-term NIV use in this population, and whether they differ from those for other children using NIV, is important for informing individualized treatment as well as fiscal health policy. This study aims to systematically review the current evidence on this topic.

Methods: This systematic review is an extension of a scoping review. The search strategy used Medical Subject Headings and free-text terms for “child” and “non-invasive ventilation” in MEDLINE (Ovid), Embase (Ovid), CINAHL (Ebsco), Cochrane Library (Wiley), and PubMed were systematically searched for the period of 1990-2019. Included studies examined NIV use for at least three months in three or more children with Down syndrome.

Results: 21 articles met inclusion criteria and included 369 children with Down syndrome. Designs were mostly observational. Only 7 studies were undertaken exclusively in children with Down syndrome. Of all children using long-term NIV, children with Down syndrome were found to represent 27%. This review did not identify any studies that directly compared long-term NIV use in children with Down syndrome to those without. Among children with Down syndrome, long-term NIV use was mainly used for the treatment of obstructive sleep apnea (OSA) and was frequently used for residual OSA following adenotonsillectomy and as a bridge to improvement in children who outgrew OSA with age. Satisfactory NIV adherence was documented in children with Down syndrome. Specific neuropsychological and cardiac benefits of long-term NIV use may be seen in this population, though data on outcomes specific to children with Down syndrome is scarce.

Conclusions: Children with Down syndrome can successfully use long-term NIV, however with no comparative studies, it is unclear whether they face more challenges with its use. With limited studies focusing on outcomes, the benefits of long-term NIV for children with Down syndrome remain difficult to define.

Chemistry Review and Analysis of Vaping Products and Respiratory Injury

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Introduction: While the Public Health Agency of Canada notes 20 cases from May 2019 to August 2020 relating to e-cigarette or vaping product use-associated lung injury (EVALI) in Canada, there are likely many more unreported cases, including non-hospitalized and asymptomatic cases. E-cigarette use or vaping exposes users to numerous aerosolized chemical species, some of which have proven to be deleterious to human health. These chemical species can include vitamin E acetate (VEA), flavourants, base / solvents (propylene glycol or vegetable glycerin), psychoactive substances, pesticides, endotoxins, metals, and pyrolysis by-products from e-cigarette heating coils.

Methods: To understand the vaping health effects of specific compounds, we first reviewed EVALI-related literature from the standpoint of known chemical species currently used in vaping products. A comprehensive literature search was performed with MEDLINE for EVALI-related human studies that were published between January 1, 2010, and May 15, 2020. This search strategy identified 832 case reports, case series, clinical trials, and in-vitro laboratory studies. From this group, 71 records were examined in greater detail. Afterwards, we began developing a method to detect carbonyl compounds in vaping products utilizing 2,4-dinitrophenylhydrazine (DNPH) derivatization, followed by high performance liquid chromatography (HPLC) analysis.

Results: Although the chemical composition and toxicology of vaping products have largely been characterized, the physiological effects of the chemical interactions between various constituents of vaping products and the generation of new species remain inconclusive. Our preliminary analytical method detected numerous compounds found in different vaping products, including cinnamaldehyde and vanillin. Both compounds, when inhaled, may cause respiratory irritation and inflammation.

Conclusion: Given the rapid rise in the popularity of vaping and e-cigarettes, there is a need for further research. Developing a comprehensive understanding of the chronic health effects of vaping through randomized controlled trials and physiological studies is prudent and necessary to reduce the long-term impacts on users and the health care system.

Prognostic Implications of Abnormal Left-right Lung Perfusion Differential on Routine Post-transplant Ventilation-perfusion Scans

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Purpose: Lung ventilation-perfusion (VQ) scans can be used to diagnose pulmonary thromboembolic disease as well as for surgical lung resection planning and monitoring after lung transplant. The long-term implications of abnormalities on routine post-transplant studies however are unknown. The relative lung perfusion distribution obtained from VQ scans provides an assessment of the pulmonary blood flow with a 55%-45% right-to-left differential typically considered the threshold of normal. We hypothesized that unbalanced relative lung perfusion on 3-months post-transplant VQ scan would be associated with poorer long-term survival and secondarily with increased frequency or severity of chronic lung allograft (CLAD) and baseline lung allograft dysfunction (BLAD).

Methods: We studied all double lung transplant recipients in our program between 2004-2016. The primary variable of interest was perfusion differential, with an abnormal threshold $\geq 10\%$ on 3-months VQ scan. We used Kaplan Meier estimates with log rank tests to assess the association between lung perfusion differential and survival as well as CLAD development. Fisher's Exact test and Cochran-Armitage trend testing were used to evaluate the relationship between perfusion differential and baseline lung allograft dysfunction (BLAD, defined as failure to achieve both FEV1 and FVC $\geq 80\%$ predicted on 2 consecutive tests ≥ 3 weeks apart).

Results: Of 340 patients who met inclusion criteria, 169 (49%) had a relative perfusion differential of at least 10% on their 3-months VQ scans. Patients with increased perfusion differential had longer hospital stays (24 days vs. 21 days; $p=0.004$), poorer overall survival (Figure 1, $p=0.011$) and increased CLAD onset ($p=0.012$). Increased perfusion differential was also associated with increased risk of BLAD (42% vs. 32%; $p=0.043$) and higher grade BLAD ($p=0.006$).

Conclusion: Abnormal relative lung perfusion differential is common after lung transplant and associated with increased risk of death, poor post-transplant baseline function and CLAD. We feel this measurement warrants further exploration as a potential predictor of future lung dysfunction and its related risk, particularly the mechanisms and risk factors.

Prognostic Significance of Asymptomatic Pulmonary Embolism on Routine Ventilation-Perfusion Scans after Lung Transplantation

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Purpose: Asymptomatic pulmonary embolism (PE) is a challenging clinical entity with unclear treatment implications. This is also true of PE detected on routine studies after lung transplant where clot may be donor derived. Our program performs routine ventilation-perfusion (VQ) scans at 3-months post-transplant to establish baseline airway and vascular function but in some cases, these are positive for PE. We hypothesized that asymptomatic PE in this context would carry a benign prognosis irrespective of therapy.

Methods: We studied VQ scans obtained routinely at 3-months post-transplant from double lung transplant recipients in our program between 2004-2016. The risk group was patients whose studies were interpreted as high probability for PE. We used chi square testing for the relationship between PE with 1-year survival. We also used Kaplan Meier analysis with log rank testing and t-tests for the association with overall survival and peak forced expiratory volume in 1 second (FEV1) percent predicted.

Results: 373 patients met inclusion criteria, of whom 35 (9%) had VQ scans interpreted as high probability for PE. The PE group were less likely to have had severe primary graft dysfunction (3% vs. 19%; $p=0.03$) but were otherwise similar to patients without PE. 7 patients in the PE group (20%) were treated with therapeutic anticoagulation and the remainder treated expectantly. Patients with PE had similar 1-year survival (100% vs. 98%, $p=1.00$), overall survival (log rank $p=0.90$) and peak FEV1% predicted (94% [SD 20%] vs. 92% [SD 21%]; $p=0.58$). We observed no differences between treated and untreated PE.

The Effects of Pulmonary Rehabilitation Following an Acute Exacerbation of COPD on Vascular Health

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Introduction: Patients with chronic obstructive pulmonary disease (COPD) experience increased risk for cardiovascular disease, which is potentiated during an acute exacerbation (AE). The pathophysiology of this is not well understood; however, previous research suggests that impairments in vascular function may develop with an AECOPD. Early mobilization in patients following an AECOPD may protect against maladaptive vascular remodelling associated with prolonged bedrest. Pulmonary rehabilitation (PR) is often prescribed for patients with stable COPD and there is some evidence that PR can improve markers of vascular function such as pulse wave velocity; however, the evidence for the impact of PR on vascular function following an AECOPD is limited. The purpose of this study was to determine whether PR improves vascular function following an AECOPD. As a secondary outcome, we aimed to determine if physical activity (PA) modulated changes in vascular function.

Methods: Twenty-five patients with an AECOPD recently discharged from hospital ($FEV_1 = 46\%$ predicted, Age = 66yrs, BMI = 29kg/m^2) were enrolled in an 8-week PR program. Sixteen patients with an AECOPD ($FEV_1 = 45\%$ predicted, Age = 69yrs, BMI = 27kg/m^2) not attending PR served as controls. Primary outcomes included: change in carotid-radial pulse-wave velocity (PWV_{CR} , Complior), change in brachial artery diameter (flow-mediated vasodilation, FMD) and step count (FitBit). Data was collected 14 days following discharge (baseline) as well as following PR completion (post) (and at that same time point in the control group).

Results: Baseline PWV_{CR} was not significantly different between groups ($AE_{Rehab}=8.3 \pm 2.1\text{m/s}$ vs. $AE_{Control}=7.2 \pm 1.1\text{m/s}$, $p=0.07$). FMD was not significantly different between AE_{Rehab} and $AE_{Control}$ ($5.3 \pm 6.2\%$ increase vs. $3.9 \pm 7.4\%$ increase, $p=0.70$). PR did not significantly improve PWV_{CR} ($-0.3 \pm 2.0\text{m/s}$) or FMD ($+1.1 \pm 7.3\%$ increase); however, PWV_{CR} did significantly increase in $AE_{Control}$ ($+1.3 \pm 1.9\text{m/s}$, $P=0.029$). Step count was not significantly different at baseline ($AE_{Rehab}=2255 \pm 2097$ steps/day vs. $AE_{Control}=1462 \pm 1564$ steps/day, $p=0.54$) and post ($AE_{Rehab}=1871 \pm 1762$ steps/day vs. $AE_{Control}=2028 \pm 1851$ steps/day, $p=0.84$). Multiple regression analysis showed that changes in PWV_{CR} were independent of step count.

Conclusion: Initial results would suggest that early PR in patients with an AECOPD may play a role in protecting against vascular stiffening; however, further research is required. Moreover, PA does not appear to modulate changes observed from PR. Future analysis will examine the impact of PR on systemic inflammatory markers to determine if changes in systemic inflammation are driving vascular function.

Peripheral Diffusion Limitation in Individuals with Mild Chronic Obstructive Pulmonary Disease

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Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by partially reversible airflow obstruction, increased exertional dyspnea, and exercise intolerance. Though patients with COPD experience a respiratory limitation to exercise, literature suggests a peripheral muscle diffusion limitation may also be present. Peripheral muscle oxygen extraction dysfunction would manifest as an increased partial pressure of oxygen in mixed venous blood (PvO_2), which may lead to increased leg discomfort and exercise intolerance. The purpose of this study was to determine if patients with COPD have an elevated PvO_2 compared to controls during exercise, suggesting a peripheral muscle diffusion limitation.

Methods: 12 patients with mild COPD (FEV_1 : $87\% \pm 4$) and 13 healthy subjects who were part of a larger study in our laboratory took part in this sub-study. Participants completed a standard pulmonary function test and cardiopulmonary exercise test. Oxygen consumption was measured using breath by breath gas analysis, and cardiac output was estimated using impedance cardiography. Arterial oxygen saturation was monitored and recorded with a pulse oximeter. PvO_2 was calculated based on the Fick equation, using acquired oxygen consumption, arterial oxygen saturation, cardiac output data, and hemoglobin data estimated based on normative.

Results: Patients with COPD had significantly lower exercise capacity than controls (Control: 33.7 ± 2.4 vs. COPD: 20.4 ± 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$; $p < 0.001$). There was no difference in cardiac output at submaximal exercise between the two groups (Control: 6.81 ± 0.23 vs COPD 6.73 ± 0.25 $L \cdot min^{-1}$; $p = 0.830$); however, submaximal arterial oxygen saturation values were lower in COPD (Control: 97 ± 1 vs COPD: $95 \pm 1\%$; $p = 0.026$). No difference in PvO_2 at submaximal exercise was determined between the two groups (Control: 18.85 ± 1.26 vs COPD: 21.05 ± 1.20 mmHg; $p = 0.223$).

Conclusions No difference was observed in mixed venous O_2 between mild COPD patients and age-matched controls during exercise, suggesting that a peripheral muscle diffusion limitation does not explain the reduced exercise tolerance in mild COPD.

It's All About That Trach! - Using a Modified Delphi Approach to Developing Pediatric Tracheostomy Teaching Tools

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Introduction: Pediatric tracheostomy care is intimidating; regular and emergency care are critical skills. Tracheostomy care training is vital for pediatric patients as they have multiple people involved in their care and are dependent on their tracheostomy tubes. An AHS team is developing an informational tool, the “Tracheostomy Journey”, to help families and healthcare providers understand and communicate clearly about pediatric tracheostomy. A needs assessment identified consistent, universal multimodal teaching and communication tools for families, trainees, hospital & home care providers as a primary need. Consistency in training will also improve communication between caregivers and families of these children.

Method: This project provides a structured approach to developing training modules that address learning goals for safe, consistent pediatric tracheostomy care. The project consisted of two components: 1) Update and consolidate basic care checklists completed by families before hospital discharge. 2) Formalize current unstructured emergency training while building new resources to teach families, hospital staff and trainees through goal-oriented simulations.

Results: We consolidated 7 Home Care tracheostomy care checklists and developed 22 simulations to teach specific skills for tracheostomy care to families and clinical teams, incorporating input from multiple stakeholders to consolidate and unify content. The materials emphasize confidence building as learners master each skill. Each module consists of a scenario, preceptor script and debriefing materials to ensure the learning point is addressed. Each is scripted to allow filming so trainees can review scenarios as needed. Simulations were reviewed by physicians, allied health and trainees.

Conclusion: The materials and supporting documents are set up for evaluation by an expert team via a modified Delphi process, and beta testing with trainees including knowledge and confidence assessment before and after training after training. These tools are ready for employment and anticipated to improve teaching and communication for families and trainees caring for children with tracheostomy.

Regulation of Proteinase-Activated Receptor-2 by Pro-Inflammatory Cytokines in Airway Epithelial Cells

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Introduction: Airway Epithelial Cells (AECs) are important in asthma pathogenesis. When activated by various inhaled particles, these cells will release inflammatory mediators into the airways. Proteinase-Activated Receptor-2 (PAR-2) is highly expressed on AECs and is implicated in the sensitization and development of asthma. PAR-2 activation results in cell-induced inflammatory effects in the airways. Prior work in our lab has found PAR-2 is *upregulated* in asthma ex vivo and by cellular stress in vitro. PAR-2 regulation mechanisms in AECs are not well understood. We hypothesize that pro-inflammatory cytokines will affect PAR-2 expression in human AECs.

Methods: Beas-2B cells, a human transformed AEC line, were grown on tissue culture plates until 90% confluent and then cultured for 24 hours in the presence (normal condition) or absence (stressed cells) of growth factors. Cells were then activated for 24 hours with three cytokines, interleukin (IL)-13, IL-4, or tumor necrosis factor (TNF), that are all involved in the inflammatory response of the airways. Various concentrations of each cytokine were used for activation. Cells were then lysed, and RNA was extracted (TRizol) and then reverse transcribed. Quantitative polymerase chain reaction was performed for PAR-2, with GapDH as the housekeeping gene. Absolute PAR-2 copy numbers were given, and data was then analyzed by one-way ANOVA and independent T-test ($\alpha=0.05$).

Results: IL-4 and IL-13 analysis indicated no effect on PAR-2 expression in normal Beas-2B cells. TNF could not be analyzed (n=2) however appeared to have similar results in normal Beas-2B cells. Stressed cells showed increased PAR-2 expression, which was previously shown in the lab. IL-13 (20ng/ml) confirmed past data, significantly downregulating PAR-2 expression in stressed Beas-2B cells; IL-13 at 0.8ng/ml had the same effect. All concentrations of TNF and IL-4 significantly downregulated PAR-2 expression in stressed Beas-2B cells.

Conclusion: Pro-inflammatory cytokine stimulation had no effect on PAR-2 expression in normal AECs, but downregulated PAR-2 expression in stressed cells. Reasons for these cytokine's differential effect is unclear. Postulated mechanisms may include the use of different signalling pathways in the two conditions or altered sensitivity to these cytokines when cells are stressed. Future work will help us understand these mechanisms better. Improving knowledge on this pathway is important as it may be related to asthmatic regulation, which could have implications for future clinical work.

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