Annual Research & Award Day
Division of Respirology 2022

Wednesday October 12, 2022
9:00-17:00

Munk School of Global Affairs
1, Devonshire place

www.respirologyresearch.com

Division of Respirology
Department of Medicine
Faculty of Medicine

Contact info:
respirology.research.day@gmail.com

UNIVERSITY OF TORONTO

PROGRAM – Annual Research & Award Day 2022 – October 12, 2022

8.30 Coffee & Breakfast. 

8.30 Posters setting.

9.00 Opening of the Respirology Research Day: Gaspard Montandon.

9.05 Director of the Division of Respirology – **Dr. Chung-Wai Chow**.

9.15 SESSION 1 – Clinical Sciences

9.30 **Albert Cheng.** The impact of donor-recipient sex match on lung function after lung transplant (abstract #6).

9.45 **Shoichiro Yatsu.** Comparison of cardiac structure and function of patients with heart failure with reduced ejection fraction with and without sleep-disordered breathing (abstract #31).

10.00 **Kevin Zhang.** Comparing bronchoalveolar lavage microbiological culture positivity between right versus left single lung transplants (abstract #30)

10.15 **Anastasiia Vasileva.** Characterization of chronic lung allograft dysfunction (CLAD) at time onset using respiratory oscillometry (abstract #27)

10.30 Coffee Break 

11.00 SESSION 2 – Basic Sciences

11.00 **Andreea Furdui**. Periaqueductal gray somatostatin-expressing cells constitute a key circuit modulating breathing and respiratory depression by opioids (abstract #12).

11.15 **Olivia Mekhael.** Transcriptomic profiling of small airway epithelium club cells in chronic lung allograft dysfunction (abstract #18).

11.30 **Sumiha Karunagaran**. Investigation of pleural cavity B cells in a minor alloantigen-mismatched mouse orthotopic lung transplant model (abstract #15).

11.45 **Ke Bei.** Evidence for a gene expression program promoting regulatory T cell dysfunction in the chronically rejected lung allograft (abstract #4).

12.00-13.30 Lunch break 

12.30 Poster session - Cloister

13.30 KEY-NOTE SPEAKER:

Dr. Estelle Gauda, M.D.

Professor of Pediatrics, University of Toronto
Head, Division of Neonatology, The Hospital for Sick Children

Lifelong respiratory consequences of prematurity

14.30 SESSION 2 – Health Sciences

14.30 **Amanda Mac**. Deep Learning Using Multi-Layer Perceptron Improves the Diagnostic Acumen of Spirometry (abstract #17).

14.45 **Stephanie Nevison**. Unnecessary inhaler use in interstitial lung disease: a needs assessment (abstract #21).

15.00 **Nour Hanafi**. Can early lung function measurement predict baseline lung allograft dysfunction (BLAD)? (abstract #14).

15.15 **Rozhan Momen.** Evaluation of Frailty in Patients with Pulmonary Hypertension (abstract #19).

15.15 Coffee break 

15.45 Awards and Prizes of the Division of Respirology

Organizers:
Dr. Gaspard Montandon
Ms. Rhiannon Davies

Judges:
Dr. Dmitry Rozenberg
Dr. Jean-Phillipe Rousseau
Dr. Stephen Juvet

Awards of Division of Respirology

Jae Yang Award 2021-22 recipient:

Shaun Ong

Faculty Teacher Award 2021-22 recipient:

Jolene Fisher

Faculty Excellence in Research Award 2021-2022:

Lianne Singer

Outstanding Research Trainee Award 2021-2022:

Stacey Butler
(supervisor: Andrea Gershon)

KEY-NOTE SPEAKER

Estelle B. Gauda, M.D.

Professor of Pediatrics,
University of Toronto
Head, Division of Neonatology,
The Hospital for Sick Children
Women's Auxiliary Chair of
Neonatology,
The Hospital for Sick Children
Director,
Toronto Center for Neonatal Health
Senior Associate Scientist,
SickKids Research Institute
Board-Certified Neonatologist

Dr. Gauda obtained her M.D. from the University of Iowa in 1982 and completed a residency in Pediatrics at St. Louis Children's Hospital in 1985, followed by a fellowship in Neonatal-Perinatal Medicine in 1987 at Rainbow Babies and Children's Hospital, Case Western University. Dr. Gauda joined the faculty at Johns Hopkins and remained at Johns Hopkin for 30 years, becoming a Professor of Pediatrics and Senior Associate Dean for Faculty Development. In 2017, she was recruited to The Hospital for Sick Children to be the Head of the Division of Neonatology, Professor of Pediatrics at the University of Toronto and Senior Associate Scientist at the SickKids Research Institute.

Dr. Gauda is a physician-scientist with several research interests that include mechanisms that control breathing during development, alternative treatment paradigms for opioid withdrawal in newborn infants, and novel therapies for the treatment and prevention of lung disease in premature infants. She is the author and co-author of over 90 peer-reviewed articles, reviews and chapters on both research topics. She is the recipient of multiple NIH awards and have had leadership positions in the Society for Pediatric Research, American Thoracic Society, and Society for Neuroscience, the International Society of Arterial Chemoreceptors.

Dr. Gauda is passionate about mentoring and fostering the development of the next generation of physicians and scientist and has leveraged her position and her basic science laboratory to achieve this goal. Moreover, she is committed to increasing the pipeline of students and trainee of color and from marginalized background through longitudinal mentoring over the years. She was recently recognized for her contributions to mentoring and was the recipient of the Johns Hopkins Alumni Mentoring Award in 2020.

Authors' List (alphabetic order)

Abstract #	Name		Email	Poster #
1	Noor	Al Kaabi	noor.alkaabi@mail.utoronto.ca	**P1**
2	Victoria	Arrandale	victoria.arrandale@utoronto.ca	**P2**
3	Kayla	Baker	kayla.schumacker@mail.utoronto.ca	**P3**
4	Ke	Bei	kefan.bei@uhnresearch.ca	**O**
5	Stacey	Butler	stacey.butler@utoronto.ca	**P4**
6	Albert	Cheng	alb.cheng@mail.utoronto.ca	**O**
7	Denny	Choi	denny.choi@mail.utoronto.ca	**P5**
8	Tania	Da Silva	t.dasilva@mail.utoronto.ca	**P6**
9	Lee	Fidler	lee.fidler@utoronto.ca	**P7**
10	Lee	Fidler	lee.fidler@utoronto.ca	**P8**
11	Anne	Fu	anne.fu@mail.utoronto.ca	**P9**
12	Andreea	Furdui	andreea.furdui@mail.utoronto.ca	**O**
13	Xiaowei	Gao	viviannegao@hotmail.com	**P10**
14	Nour	Hanafi	nour.hanafi@mail.utoronto.ca	**O**
15	Sumiha	Karunagaran	sumiha.karunagaran@uhnresearch.ca	**O**
16	Haruna	Kitazawa	haruna.kitazawa@uhnresearch.ca	**P11**
17	Amanda	Mac	amanda.mac@uhnresearch.ca	**O**
18	Olivia	Mekhael	olivia.mekhael@uhnresearch.ca	**O**
19	Rozhan	Momen	rozhan.momen@uhnresearch.ca	**O**
20	Maha	Munawar	maha.munawar@mail.utoronto.ca	**P12**
21	Stephanie	Nevison	stephanie.nevison@mail.utoronto.ca	**O**
22	Cynthia	Nohra	cynthia.nohra@mail.utoronto	**P13**
23	Honami	Ota	honami.ota@uhnresearch.ca	**P14**
24	Peter	Rassam	peter.rassam@mail.utoronto.ca	**P15**
25	Jean-Philippe	Rousseau	jean-philippe.rousseau@unityhealth.to	**P16**
26	Kimia	Sheikholeslami	kimia.sheikholeslami2@uhn.ca	**P17**
27	Anastasiia	Vasileva	anastasiia.vasileva@uhnresearch.ca	**O**
28	Lena	Xiao	lena.xiao@sickkids.ca	**P18**
29	Kevin	Zhang	cykevin.zhang@mail.utoronto.ca	**P19**
30	Kevin	Zhang	cykevin.zhang@mail.utoronto.ca	**O**
31	Shoichiro	Yatsu	Shoichiro.Yatsu@uhn.ca	**O**
32	Jan	Lim	jan.lim@mail.utoronto.ca	**P20**

P = poster presentation

O = oral presentation

Abstracts:

Abstract #1

Respiratory Symptoms, Quality of Life, and Symptom Management in Ehlers-Danlos Syndrome/ Generalized-Hypermobility Spectrum Disorders

Noor Al Kaabi (1,2,3), Encarna Camacho (1,3), Rozhan Mohmen(1,2,4), Sahar Nourouzpour(1), Maxwell Slepian (2,3,5), Maxim Rachinsky(3), Darlene Reid (6,7), Laura Lopez (3), Laura Mcgillis (3), Pranab Kumar (6,8), Tania DiRenna (8), Fatmah Al Habeeb (8), Anna Day (8), Daniel Santa Mina (2,3,4,5) , Nimish Mittal (2,3,5) , Hance Clarke (2,3,5) , Dmitry Rozenberg (1,2,3).

noor.alkaabi@mail.utoronto.ca

1. Division of Respirology, University Health Network, Toronto General Research Institute.
2. Temerty Faculty of Medicine, University of Toronto.
3. GoodHope Ehlers-Danlos Syndrome Program.
4. Faculty of Kinesiology and Physical Education.
5. Department of Anesthesia and Pain Management.
6. KITE - Toronto Rehab.
7. Physical Therapy, University of Toronto.
8. Women's College Hospital, Toronto.

Introduction: Ehlers-Danlos Syndrome (EDS) and Generalized Hypermobility Spectrum Disorders (G-HSD) are connective tissue disorders with multi-systemic manifestations (e.g musculoskeletal, gastrointestinal, and respiratory). Respiratory symptoms such as dyspnea and chest tightness are commonly reported, but have not been well characterized in EDS/G-HSD, and patients report unmet symptom management needs. Identifying the clinical impact of respiratory symptoms and management priorities for EDS/G-HSD patients may improve their care.
Objectives: 1) To characterize respiratory symptoms, health-related quality of life (HRQoL) and physical activity (PA) in EDS/G-HSD. 2) Identify management priorities for respiratory symptoms.
Methods: A cross-sectional study using patient reported outcome measures (PROMs), Fitbits and individual semi-structured interviews. Adult (≥18 years) EDS/G-HSD patients receiving care at Toronto General Hospital with respiratory symptoms or pulmonary conditions were included. St. George's Respiratory Questionnaire (SGRQ), Medical Research Dyspnea (MRC) Scale and 18-item dyspnea scale were used. PA levels were characterized over a 7-day period with Fitbits. Qualitative description was used to explore patients' symptoms and management needs with emerging themes identified.
Results: 19 EDS/G-HSD patients completed respiratory PROMs (Age 36 ± 12 years; 79% females). 35% of participants reported MRC ≥ 3 and 47% described unsatisfactory inspiration and chest tightness. The mean total score on the SGRQ was 36.6±20.8 (symptoms: 49.0±23.2; activity: 49.0±29.1; impact 24.7±18.6). The mean daily step count was 5322±3307 (n=10). Emerging themes identified that dyspnea was the main limiting symptom in daily activities and that respiratory symptoms were the most prioritized. Given the multi-systemic nature of symptoms,

participants described balancing management strategies that relieved respiratory symptoms, but exacerbated other symptoms (i.e. avoiding hot baths due to dyspnea, which help relieve musculoskeletal pain).
Conclusion: Preliminary observations suggest that EDS/G-HSD experience increased respiratory symptoms, impaired HRQoL, and reduced PA levels. Further investigation into the association between specific respiratory symptoms, HRQoL and management strategies is ongoing.
Funding: Ehlers-Danlos Syndrome UHN Foundation Grant, CIHR Canada Graduate Scholarship and the Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine.

Abstract #2

Silicosis in Ontario from 1996-2019

Victoria H Arrandale (1,2), Yizhi Zhang (1), Kruti Mehta (1), Nikhil Rajaram (1,3), Ambrose Lau (1,4), D. Linn Holness (1,5) Susan M Tarlo (1,4,5)

1. University of Toronto.
2. Occupational Cancer Research Centre, Toronto.
3. Ontario Ministry of Labour, Toronto.
4. University Health Network – Toronto Western Hospital, Toronto,
5. Unity Health Toronto – St Michael's Hospital, Toronto.

victoria.arrandale@utoronto.ca

Introduction & Objectives: Silicosis, a fibrotic lung disease caused by exposure to respirable crystalline silica, was historically common among miners. In recent years silicosis has been reported among workers in the artificial stone countertop industry. The objective of this study was to describe the trends in the incidence of silicosis in Ontario, Canada using administrative health data.
Methods: Administrative health data for the province of Ontario between 1993 and 2019 were analyzed. The case definition required ≥2 outpatient physician visits within 24 months (ICD9 502, ICD10 J62). Cases identified from 1993-1995 were considered prevalent and removed from analysis. Incidence rates per 100,000 persons were calculated by time-period, age, sex, and region. Comparative analyses were conducted for pulmonary fibrosis (PF) (ICD9 515, ICD10 J84) and asbestosis (ICD9 501; ICD 10 J61).
Results: During the study period there were 444 identified cases of silicosis, 2719 cases of asbestosis and 59,228 cases of PF. Silicosis incidence rates decreased from 0.42 cases per 100,000 in 1996-2000 to 0.06 per 100,000 people in 2016-2019. A similar trend was observed for asbestosis (1.66 to 0.51 per 100,000 persons. However, the incidence rate of PF increased from 11.6 to 33.9 per 100,000 persons. Incidence rates for all outcomes were higher among men and older adults.
Conclusion: A decreasing incidence of silicosis was observed over the study period (1995-2019) for all age groups, likely due to improved prevention. In contrast, the incidence of PF was observed to increase over the study period, consistent with findings from other jurisdictions. The increase in PF incidence may be due in part to improved detection, misclassification, or billing incentives during the study period. While cases of silicosis have been recorded among artificial stone workers in Ontario, Canada these cases do not seem to have impacted the population rates.

Abstract #3

Role of brainstem inhibitory neurons in the control of breathing

Kayla S. Baker (1, 2), Carolina Scarpellini (2), Gaspard Montandon (1, 2, 3)

1. Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada.
2. Keenan Research Center for Biomedical Science, St. Michael's Hospital, Unity Health Toronto, Toronto.
3. Division of Respirology, Department of Medicine, University of Toronto, Toronto.

kayla.schumacker@mail.utoronto.ca

Introduction: Breathing is an essential and automatic process that is critical to maintaining metabolism in most vertebrates. The brainstem controls breathing by signaling to the diaphragm to initiate inhalation and exhalation. The generation of respiratory rhythms relies upon inhibitory feedback between inspiratory and expiratory neurons within and between brainstem nuclei. At the core of the brainstem respiratory network is the preBötzinger Complex (preBötC), a collection of neurons critical to generating breathing and contains excitatory and inhibitory cells involved in the coordination of inhalation and exhalation. One of the main types of inhibitory neurons in the brain is known as γ-aminobutyric acid (GABA) neurons, but the role of GABA cells in regulating respiratory rhythm is unknown. Many drugs used in healthcare target the GABAergic neurons in the brain and can cause respiratory depression such as benzodiazepines and anesthetics.
Objective: It is critical to understand how the preBötC GABA cells are involved in our respiratory rhythms and we aim to identify their role in the control of breathing.
Methods: In order to study GABA neuron activity within the respiratory cycle, we used optogenetics – a technique that uses light to control cell activity – to activate and inhibit preBötC GABA while measuring changes in breathing. To measure breathing we recorded diaphragm and genioglossus activity in anesthetized mice, and in freely behaving mice we used whole-body plethysmography.
Results: PreBötC GABA neuron activation decreased the respiratory rate by prolonging the expiratory time in both anesthetized and freely behaving mice. Inhibition of preBötC GABA cells increased the respiratory rate by shortening the expiratory time.
Conclusion: These combined data suggest that the preBötC GABA neurons are expiratory. By identifying how these neurons control breathing, we will have a better understanding of what is occurring when breathing is depressed, such as with benzodiazepines or anesthetics.

Abstract #4

Evidence for a gene expression program promoting regulatory T cell dysfunction in the chronically rejected lung allograft

Ke Bei (1, 5), Allen Duong (1, 4), Sajad Moshkelgosha (1), Tereza Martinu (1, 2, 3, 4, 5), Stephen Juvet (1, 2, 3, 4, 5)

kefan.bei@uhnresearch.ca

1. Toronto Lung Transplant Program, Latner Thoracic Research Laboratories, Toronto General Hospital Research Institute, University Health Network, Toronto.
2. Division of Respirology, Department of Medicine, University of Toronto
3. Ajmera Transplant Centre, University Health Network
4. Institute of Medical Science, University of Toronto
5. Department of Immunology, University of Toronto

Introduction. The 10-year survival following lung transplantation is 32% due to the development of chronic lung allograft dysfunction (CLAD) – a progressive fibrosis of the airways and/or parenchyma driven by anti-donor (allo) immunity, for which new preventive therapies are needed. One candidate is regulatory T cell (Treg, subset of CD4+ T cells that maintain immune homeostasis) therapy. Allograft occupancy by functional Tregs is required for graft acceptance in animal models and is associated with good allograft outcome in humans. We hypothesize that CLAD is associated with intra-graft Treg dysfunction.

Methods. We generated 3' single cell RNA sequencing (scRNAseq) data from CLAD lungs obtained at the time of re-transplantation or autopsy, along with peripheral blood mononuclear cells (PBMC) from the same individuals (n=6). In addition, a 5' gene expression library generated from sorted T and B cells was analyzed. Tregs were identified as FOXP3 RNA > 0. DEseq2 was used to compare gene expression between lung and PBMC Tregs, with significantly differentially regulated genes defined as those with $p < 0.05$ and a log2 fold-change cut-off of 0.5.

Results. Comparison of CLAD lung and paired PBMC Tregs found RBPJ, SRGN, BATF, and both TNFRSF4 (OX40, a negative regulator of Tregs), and TNGFRSF18 (GITR, function-associated marker) were upregulated in lung Tregs compared to PBMC Tregs. JUNB, a component of the AP-1 pathway shown in murine studies to be required for efficient Treg function, was downregulated in lung Tregs. In addition, suppressor of cytokine signaling 3 (SOCS3), Kruppel-like factor 2 (KLF2) and ZFP36 were found to be higher in PBMC Tregs (Figure 1).

Conclusion. These contrasting observations may indicate a dynamic balance between factors promoting Treg function and those driving dysfunction in the chronically rejected lung allograft. Further work will be needed to determine the functional impacts of these observations.

Acknowledgements: Latner Thoracic Research Laboratories; Princess Margaret Genomics Facility.

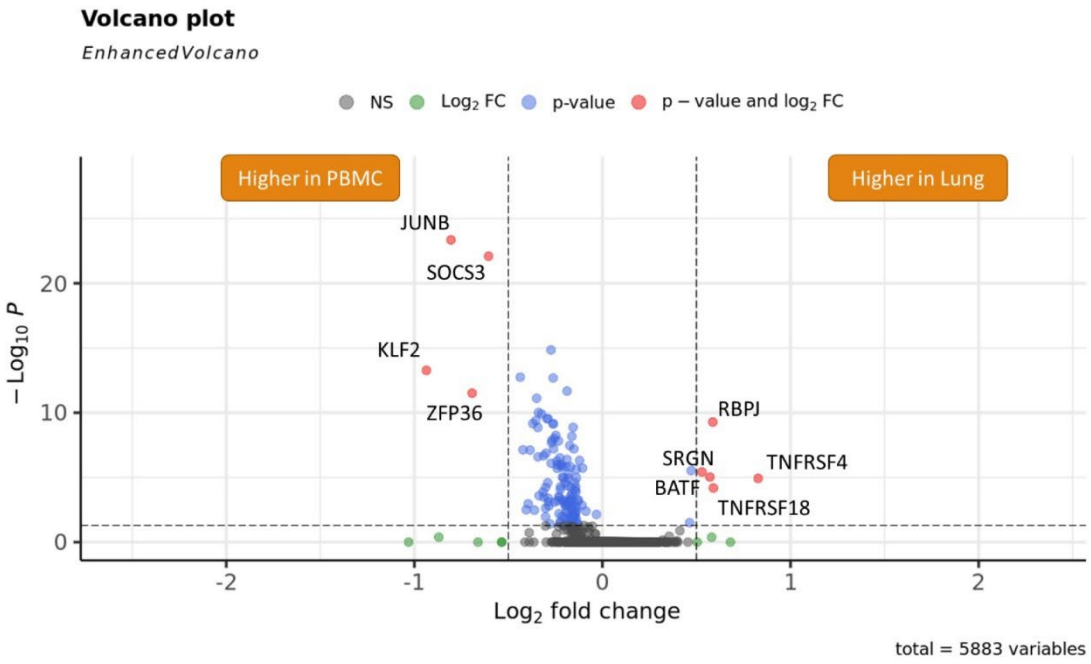


Figure 1. Volcano plot displaying DESeq2 analysis of cells with FOXP3 > 0 from CLAD lung and paired PBMC samples (n=6). Data analysed via Seurat by R. p-value < 0.05 and log2 fold-change cut-off of 0.5.

Abstract #5

Impact of COPD on Symptom Burden in Stage IV Lung Cancer Patients

Stacey J Butler (1,2,3), Alexander V Louie (3), Rinku Sutradhar (2,3,4), Lawrence Paszat (2,3,4), Dina Brooks (5), Andrea S Gershon (1,2,3,4)

stacey.butler@utoronto.ca

1. Institute of Medical Sciences, University of Toronto.
2. ICES.
3. Sunnybrook Research Institute, Sunnybrook Health Sciences Centre.
4. Institute of Health Policy, Management and Evaluation, University of Toronto.
5. School of Rehabilitation Sciences, McMaster University.

Introduction: Over half of all lung cancer patients in Ontario have chronic obstructive pulmonary disease (COPD). Separately, lung cancer and COPD cause similar symptoms, including shortness of breath, cough, and fatigue. Patients who have both lung diseases may experience more severe symptoms and therefore, may have greater palliative care needs.
Methods: We conducted a population-based cohort study of stage IV lung cancer patients in Ontario diagnosed between 2009 and 2019. Symptom burden is assessed routinely among cancer patients through a province-wide initiative using the Edmonton Symptom Assessment Scale (ESAS). We included patients who completed the ESAS within 30 days of diagnosis. Coexisting COPD was ascertained using a validated case definition for health administrative data. Symptom severity (mild (3/10), moderate (4 to 6) or severe (7)) and total symptom distress (out of 90), physical (/60), and emotional symptom scores (/20) were compared between patients with and without COPD, and by sex. A standardized mean difference (SMD) > 0.1 was considered statistically significant.
Results: There were 39,732 patients with stage IV lung cancer identified, of which 11,484 patients (40% with COPD, 47% female) completed the ESAS within 30 days of diagnosis (median time: 17 days (IQR=11 to 23). Patients with COPD had marginally worse total symptom distress and physical symptom scores, compared to patients without COPD. These differences were most pronounced among females (Total distress: 32.7 ± 18.1 vs. 29.0 ± 17.5, SMD=0.21, Physical: 20.5 ± 12.9 vs. 17.6 ± 12.5, SMD=0.226). More patients with COPD reported severe shortness of breath (31% vs. 21% SMD=0.24).
Conclusions: Stage IV lung cancer patients with COPD have worse symptom burden compared to patients without COPD, particularly in females. Further research is needed to determine the impact of COPD and symptom burden on the timely receipt of palliative care in this population.
Supported by: Division of Respirology, University of Toronto, CIHR, and the Ontario Ministry of Health and Long-Term Care.

Abstract #6

The impact of donor-recipient sex match on lung function after lung transplant

Albert Cheng (1), Haruna Kitazawa (1) , Natalia Belousova (1), Anastasiia Vasileva (1) , Joyce K. Y. Wu (2) , Clodagh Ryan (1) , Chung-Wai Chow (1).

alb.cheng@mail.utoronto.ca

1. Division of Respirology,
2. Toronto General Hospital Pulmonary Function Laboratory, University Health Network

Introduction & Objectives: Biological differences exist between male and female lungs, leading to differences in spirometry measurements of lung function. Best lung function achieved post-lung transplant (LTx), as measured by spirometry, is associated with survival and is used to diagnose chronic lung allograft dysfunction (CLAD). Respiratory oscillometry (Osc) is a lung function test that is gaining interest and is sensitive to changes in lung mechanics especially in the periphery. The impact of donor-recipient sex match on lung function post-LTx is not well studied. The aims of this project are 1. To characterize the effect of donor-recipient sex match on best lung function achieved post-LTx as measured by standard pulmonary function tests (PFTs) and Osc; and 2. to determine if donor-recipient sex match is associated with CLAD.
Methods: Consecutive double LTx recipients were enrolled for Osc and standard PFTs from Sept 2017 to Mar 2020. Baseline values of 224 patients with a minimum 6 months of follow-up were compared. Stepwise multiple linear and Cox regression models assessed whether sex match was significantly associated with baseline lung function after correction.
Results: The baseline % predicted PFT metrics were similar amongst the 4 groups. In contrast, the baseline oscillometry metrics of total lung resistance (R5), ventilatory homogeneity and elastance (AX and X5) were significantly better in the donor male/recipient male group. This effect is maintained in multivariable models, where F → M transplants also showed superior measurements in aforementioned oscillometry metrics. Cox regression showed that M → F transplants were significantly more likely to develop CLAD over time.
Conclusion: The models imply that male lung recipients, regardless of donor sex, tend to show better lung mechanics than female recipients. These findings suggest that sex match may be an important consideration when evaluating optimal lung transplant donor-recipient pairs.
We thank all patients for their participation, Chow Research Group members, and the TGH Pulmonary Function Lab. This study is supported by the Lung Health Foundation, Canadian Institutes for Health Research (CIHR), the CIHR-Natural Sciences and Engineering Research Council Collaborative Health Research Programme, and the Ajmera Multi-Organ Transplant Fund. H. Kitazawa is supported by the scholarship funded by the Nakayama Foundation for Human Science.

Abstract #7

Personal exposure to air pollution during the first 3 months post transplant impacts longer term outcomes

Denny Choi (1), Michelle North (1,2.3), Musawir Ahmed (1), John Matelski (4), Lianne Singer (1,5), Joyce K. Y. Wu (1), Cheol-Heon Jeong (2,3), Greg Evans (2,3), Chung-Wai Chow (1,2,3,5)

denny.choi@mail.utoronto.ca

1. Division of Respirology, Department of Medicine, University of Toronto.
2. Chemical Engineering & Applied Chemistry, Faculty of Applied Sciences and Engineering, University of Toronto.
3. Southern Ontario Centre for Atmospheric Aerosol Research, University of Toronto.
4. Biostatistics Research Unit, University Health Network, Toronto.
5. Toronto Lung Transplant Program, Ajmera Multi-Organ Transplant Unit, University Health Network.

Introduction & Objectives: Exposure to air pollution in the early period after lung transplant is associated with lower lung function at 3 months. Our objective is to examine the impact of air pollution exposure on baseline maximal forced expiratory volume in 1s (FEV1) achieved post-transplant and long-term graft function.
Methods: Double-lung transplant recipients were prospectively enrolled into a cohort study for comprehensive indoor and personal environmental monitoring at 6- and 12-weeks post-transplant and followed longitudinally for at least one year. An exposomics approach was taken to look for associations between clinical parameters and key exposure variables were used in a Cox Proportional Hazards (CoxPH) model analysis to examine the risks of chronic lung allograft dysfunction (CLAD) and a multivariate model to identify associations between pollution exposure and a decline in baseline FEV1. Patients whose baseline FEV1s post-transplant fell below 80% were categorized as having baseline lung allograft dysfunction (BLAD).
Results: Multivariate analysis demonstrated a significant inverse relationship between personal black carbon (BC) levels and baseline FEV1 with higher levels associated with increased risk of BLAD ($p = 0.035$). The CoxPH model analysis revealed that patients (n=40) in the top half of personal BC exposure had a 2.61 times higher hazard risk than patients (n=42) with lower half of BC exposure ($p = 0.038$). The multivariate model indicated that patients with higher-than-median exposure to BC experienced 7.0% decline in % baseline FEV1 ($p = 0.035$).
Conclusions: Higher personal BC levels during the first 3 months post-transplant increased the risk of baseline lung allograft dysfunction and CLAD. Reducing BC exposure early post-transplant may help improve patient's lung function over time.
The study was funded by a grant from the Canadian Institutes for Health Research (PI: CWC). We would like to thank the participants for welcoming the research team into their homes, and the following team members in collection and processing of patient samples: Manisha Tilak, Sepehr Salehi, Xiaomin Wang, Kelsey Yang. Xinhui Wu, Yuxin Zhang, Sehrish Mahmood, Sachintana Kavindi Jayasinghe.

Abstract #8

Characterization and Reliability of Internet Resources on Pulmonary Rehabilitation for Individuals with Chronic Lung Disease

Tania Da Silva (1, 2), Ashira Lokhandwala (2, 3), Noor Al Kaabi (2, 4), Julie Semenchuk (1, 2), Gillian C. Goobie (5, 6), Encarna Camacho (7), W. Darlene Reid (8, 9), Jolene H. Fisher (7), Christopher J. Ryerson (10, 11), Dmitry Rozenberg (1, 2, 7, 12)

t.dasilva@mail.utoronto.ca

1. Temerty Faculty of Medicine, University of Toronto.
2. Toronto General Hospital Research Institute, University Health.
3. Schulich School of Medicine & Dentistry, Western University.
4. Institute of Medical Science, University of Toronto.
5. Clinical Investigator Program, Department of Medicine, University of British Columbia.
6. Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh.
7. Division of Respirology, University Health Network, University of Toronto.
8. Department of Physical Therapy, University of Toronto.
9. Interdepartmental Division of Critical Care Medicine, Toronto Rehabilitation Institute, University Health Network.
10. Department of Medicine, University of British Columbia.
11. Centre for Heart Lung Innovation, St. Paul's Hospital.
12. Toronto Lung Transplant Program, University Health Network

INTRODUCTION & OBJECTIVES. Individuals with chronic lung disease commonly use the internet as a source of health information on pulmonary rehabilitation (PR). The objective of this study was to characterize internet resources on PR, and to assess the content, readability and quality of patient-directed PR resources.
METHODS. The first 200 websites for the search term 'pulmonary rehabilitation resources and exercise' were analyzed in Google, Yahoo and Bing. Website content was assessed based on 30 key components of PR from the 2021 international consensus guidelines. Website quality was determined using DISCERN, JAMA benchmarks, and Global Quality Scale (GQS). Parametric and non-parametric tests, and multivariable linear regression models were used to assess the association between website characteristics, and content and quality metrics.
RESULTS. A total of 70 PR websites were identified with the two most common categories being scientific resources (38%) and foundation/advocacy organizations (33%). The average reading grade level of websites was 11±3. PR content varied across websites (17.8±5.4 out of 30). Most websites focused on traditional modalities of aerobic (96%) and resistance training (87%), in contrast to inspiratory muscle training (19%) and balance exercises (16%). Safety considerations were infrequently discussed. Several websites provided education focused on smoking cessation (61%), breathing strategies (59%), and nutrition (57%), with fewer websites addressing self-efficacy (40%), physical activity (37%), or motivation (19%). Median DISCERN and GQS score were 4 (IQR 3-4) and 3 (IQR 2-4) out of 5, respectively, representing moderate-good quality. Foundation/advocacy websites had higher content, DISCERN, and GQS scores compared to other websites.

CONCLUSION. PR content varied significantly across websites and only partially captured items outlined in the PR consensus guidelines. Foundation/advocacy websites had the highest quality metrics; however, the higher-than-recommended reading levels may compromise patient comprehension and utilization. This study provides critical insight on the current state of online PR health-related information for the development of future resources.
Funding: Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine and the University of Toronto CREMS Summer Program.

Abstract #9

Early interstitial lung disease in rheumatoid arthritis: an observational study of risk factors and mortality in Ontario, Canada

Lee Fidler (1, 2, 3), Jessica Widdifield (4, 5, 6), Jolene Fisher (2, 3), Shane Shapera (2, 3), Andrea S. Gershon (1, 2, 4, 6)

lee.fidler@utoronto.ca

1. Division of Respirology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto
2. Division of Respirology, Department of Medicine, University of Toronto.
3. Division of Respirology, Department of Medicine, University Health Network.
4. ICES, Toronto.
5. Holland Bone & Joint Research Program, Sunnybrook Research Institute, Toronto.
6. Institute of Health Policy, Management & Evaluation, University of Toronto.

Introduction and Objectives: Interstitial lung disease (ILD) can be an early manifestation of rheumatoid arthritis (RA). We aimed to: (1) determine patient factors associated with RA-ILD development early in the RA disease course and (2) describe patient outcomes (lung biopsy, transplantation and mortality) in patients with early versus late onset RA-ILD.
Methods: We performed a retrospective observational study using health services data from Ontario, Canada. We identified RA patients between 2000 and 2018 using the Ontario Rheumatoid Arthritis Database. Early RA-ILD was defined as ILD occurring within 1 year of RA diagnosis (before or after). Patient demographics, comorbidities (bone, pulmonary, renal and cardiovascular disease, diabetes, cancer and extra-articular manifestations) and outcomes (lung biopsy, transplantation, and mortality) were recorded. We performed multivariable logistic and cox-proportional hazards regression to evaluate for significant associations.
Results: Among 191,463 RA patients, 5832 were diagnosed with RA-ILD. Of these, 1760 (30.2%) were diagnosed with RA-ILD within 1-year, before or after RA onset. Interstitial lung disease preceded RA in 858 (14.7%) individuals, with 501 (8.6%) being diagnosed more than six months prior to RA. Older patients [OR 1.06 (95%CI 1.06-1.07), p<0.0001)], immigrants [OR 1.82 (95%CI 1.50-2.22), p<0.0001] and those with lower comorbidity [OR 1.43 (95%CI 1.17-1.74), p<0.0001] had an increased odds of early RA-ILD. Early RA-ILD was associated with increased odds for surgical lung biopsy performance [OR 1.79 (95%CI 1.12-2.84), p=0.01] and lung transplantation [OR 3.47 (95%CI 2.03-5.93), p<0.0001]. Patients with early RA-ILD had a lower adjusted hazard for all-cause mortality [HR 0.71 (95%CI 0.65-0.77), p<0.0001] than those diagnosed later following an RA diagnosis.
Conclusions: The minority of RA-ILD patients develop ILD early in their disease course. Older patients and immigrants appear to be at increased risk for early RA-ILD. Patient with early RA-ILD experienced improved survival compared to those manifesting RA-ILD later in the course of disease.

Abstract #10

Rheumatoid arthritis associated interstitial lung disease: Trends in Epidemiology and Mortality in Ontario from 2000-2018

Lee Fidler (1, 2), Jessica Widdifield (4, 5), Jolene Fisher (2, 3), Shane Shapera (2, 3), Andrea S. Gershon (1, 2, 4, 5)

Lee Fidler lee.fidler@utoronto.ca

1. Division of Respirology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto.
2. Division of Respirology, Department of Medicine, University of Toronto.
3. ICES, Toronto.
4. Holland Bone & Joint Research Program, Sunnybrook Research Institute, Toronto.
5. Institute of Health Policy, Management & Evaluation, University of Toronto.

Introduction and Objectives: The epidemiology and mortality of rheumatoid arthritis related interstitial lung disease (RA-ILD) have not been described in Canada. We aimed to describe the recent trends in RA-ILD prevalence, incidence, and mortality in Ontario, Canada.
Methods: This was a retrospective population-based study using repeated cross-sections from 2000 to 2018. We estimated annual age- and sex-standardized rates for RA-ILD prevalence, incidence and mortality.
Results: Among 191,463 RA patients identified between 2000 and 2018, 5,832 (3.0%) were diagnosed with RA-ILD. Most RA-ILD patients were women (63.9%) and ≥60 years old (76.8%) at the time of RA-ILD diagnosis. RA-ILD incidence rose from 1.6 (95% confidence interval (CI) 1.3-2.0) to 3.3 (95% CI 3.0-3.6) per 1,000 RA patients (204% relative increase, $p<0.0001$) during this time. RA-ILD incidence increased in both sexes and all age groups. The cumulative prevalence of RA-ILD increased from 8.4 (95% CI 7.6-9.2) to 21.1 (95% CI 20.3-21.8) per 1,000 RA patients (250% relative increase, $p<0.0001$), increasing in both sexes and all age groups. All-cause and RA-ILD related mortality declined in patients with RA-ILD over time [55.1% relative reduction, ($p<0.0001$) and 70.9% relative reduction, ($p<0.0001$), respectively]. In RA-ILD patients, RA-ILD contributed to the cause of death in 28% of people. Men and older patients had higher all-cause and RA-ILD related mortality.
Conclusions: In a large, diverse Canadian population, the incidence and prevalence of RA-ILD are increasing. RA-ILD related mortality is declining but remains a significant cause of death in this population.

Abstract #11

Characterization of chronic lung allograft dysfunction phenotypes using oscillometry

Anne Fu (1), Anastasiia Vasileva (1), Nour Hanafi (1), Natalia Belousova (1, 2) Joyce Wu (1, 3), Zoltan Hantos (4), Chung-Wai Chow (1, 2)

anne.fu@mail.utoronto.ca

1. Department of Medicine, Temerty Faculty of Medicine, University of Toronto.
2. Toronto Lung Transplant Program, Ajmera Multi-Organ Transplant Unit, University Health Network, Toronto.
3. Pulmonary Function Laboratory, University Health Network.
4. Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary.

Background: Chronic lung allograft dysfunction (CLAD) develops most patients after lung transplantation (LTx) and presents as two main phenotypes: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). Oscillometry (Osc) is a novel and highly sensitive pulmonary function test modality. The current study investigated whether spectral and intrabreath Osc can differentiate between CLAD-free, BOS- and RAS-CLAD.
Methods: A retrospective, cross-sectional analysis of 289 double LTx recipients enrolled between 2017 and 2021 was conducted. Osc and CLAD diagnosis was performed according to international guidelines. Multiple comparisons were investigated using appropriate statistical analysis.
Findings: CLAD-free (n=182), BOS (n=28), and RAS (n=6) have different spectral Osc patterns, with BOS and RAS resembling obstructive and interstitial lung disease respectively. The spectral Osc measurements were significantly different between the CLAD patients when compared to time-matched CLAD-free patients ($p<0.05$ for all). Pairwise comparisons showed the differences were primarily due to the BOS patients. Intrabreath Osc was also significantly different between the CLAD and CLAD-free patients in both the resistance and reactance measurements. For the RAS patients, the reactance measurement at end-inspiration (XeI) was significantly different from the CLAD-free group ($p=0.015$).
Conclusions: Spectral Osc is significantly different between the CLAD-free and BOS patients but not between CLAD-free and RAS. Intrabreath Osc, specifically XeI, was significantly different between CLAD-free and RAS, highlighting the greater information provided by intrabreath as compared to spectral Osc." The study was funded by CIHR-NSERC Collaborative Health Research Projects and Peterborough K.M. Hunter Charitable Foundation Graduate Award (AF). Dr. Hantos is supported by Hungarian Scientific Research Fund Grant K128701. We thank all the patients, Chow Lab members, and Toronto General Pulmonary Function Lab for their contributions.

Abstract #12

Periaqueductal gray somatostatin-expressing cells constitute a key circuit modulating breathing and respiratory depression by opioids

Andreea Furdui (1,2), Carolina Scarpellini (1), Gaspard Montandon (1,2,3)

andreea.furdui@mail.utoronto.ca

1. Keenan Research Centre for Biomedical Science, St. Michael's Hospital.
2. Institute of Medical Science, University of Toronto.
3. Division of Respirology, Department of Medicine, University of Toronto.

Introduction & Objectives: Breathing is essential to sustaining life and is regulated by an extensive network of neural brainstem sites. One such site is the periaqueductal gray (PAG), which contains a subpopulation of somatostatin-expressing cells that have direct reciprocal connections with the preBötzinger Complex, a respiratory rhythm-generating region. The PAG also expresses mu-opioid receptors (MORs) and may play a modulatory role in opioid-induced respiratory depression (OIRD), a potentially fatal side effect of opioid drugs. Here, we aimed to determine the role of PAG somatostatin-expressing cells in the modulation of breathing and OIRD. We hypothesized that activation of this subpopulation of cells would stimulate breathing and modulate respiratory depression by the opioid fentanyl.
Methods: Using Cre-lox recombination, we developed transgenic mice that express channelrhodopsin-2, a blue light-activated excitatory receptor, in somatostatin-expressing cells (SST-ChR2$^{+/+}$). Mice were anesthetized and electrodes were inserted to record diaphragm and genioglossus muscle activity. An optical fiber was inserted above the PAG to activate somatostatin-expressing cells using blue light and an intramuscular injection of fentanyl (5 μg/kg) was used to induce respiratory depression. *In situ* hybridization was used to determine expression of somatostatin and MOR mRNA in the PAG.
Results: We found that somatostatin and MOR mRNA were expressed in the PAG, with a subset of cells in the lateral and ventrolateral PAG co-expressing both. Preliminary findings showed that activation of PAG somatostatin-expressing cells in SST-ChR2$^{+/+}$ mice (n=4) increased respiratory rate by shortening the time between inspirations. Activation of somatostatin-expressing cells in the PAG also increased respiratory rate during respiratory depression induced by fentanyl.
Conclusion: Our preliminary findings suggest that PAG somatostatin-expressing cells may constitute a subpopulation of cells that can modulate breathing and OIRD.
Acknowledgements: Canadian Institutes of Health Research; Ontario Graduate Scholarship (AF) and St. Michael's Hospital Research Training Centre Top-Up Award (AF).

Abstract #13

Discovery of new pain therapies without respiratory depression by targeting voltage-gated calcium channels in larval zebrafish

Xiaowei (Vivianne) Gao (1, 3), Yara Zayed (1), Gaspard Montandon (1, 2)

viviannegao@hotmail.com

1. Keenan Research Centre for Biomedical Sciences. St. Michael's Hospital Unity Health Toronto.
2. Department of Medicine. University of Toronto.
3. Department of Anesthesiology. Xiangya Hospital, Central South University, Changsha, China.

Introduction: Opioids are the predominant analgesic drugs but may have limited effectiveness due to their addictive properties and abuse liability that can lead to lethal respiratory depression with overdose. The current challenges in drug discovery for pain therapies are to discover a potential drug with analgesic properties without respiratory depression. Voltage-gated calcium channels are required for many nervous system functions, and their dysfunction can give rise to pathophysiological conditions such as pain. Considering their role in pain, we aim to discover new molecular targets and calcium channel modulators to alleviate nociception using our drug discovery platform in larval zebrafish. Zebrafish have the advantage of high production of embryos and high genetic homology with humans. To measure nociception, we exposed larval zebrafish to the nociceptive stimulus formalin which elicits a behavioral escape response. We also tested the respiratory depressant effects of drugs. We identified 16 FDA-approved calcium channel inhibitors and we determined their potential to reduce the nociceptive response to formalin. One of these compounds dubbed G-compound reduced the swimming response to formalin in larval zebrafish. Importantly, G compound did not show respiratory depressant effects in larval zebrafish. We also determined whether calcium channel subunits β, γ, δ, and α2 may be valid molecular targets for new pain killers by knocking out these subunits using targeted mutagenesis with CRISPR-cas9. Overall, we showed that calcium channel inhibitors may constitute valid drug candidates to reduce nociception and potentially pain without the respiratory side effects of commonly used opioid pain killers.
Acknowledgements: Research was funded by the St. Michael's Hospital Foundation, the Canadian Thoracic Society and the J. P. Bickell Foundation. XG was funded by the China Scholarship Council.

Abstract #14

Can early lung function measurement predict baseline lung allograft dysfunction (BLAD)?

Nour Hanafi (1), Anastasiia Vasileva (1), Joyce Wu (1), Clodagh Ryan (1,2), Chung-Wai Chow (1,2,3), John Matelski (4)

nour.hanafi@mail.utoronto.ca

1. Division of Respirology, Department of Medicine, Temerty Faculty of Medicine, University of Toronto.
2. Toronto General Pulmonary Function Laboratory, University Health Network.
3. Toronto Lung Transplant Program, Ajmera Multi-Organ Transplant Unit, University Health Network, Toronto.
4. Biostatistics Research Unit, University Health Network – Toronto.

Introduction & Objectives: Lung function often improves over 6-18 months following lung transplant (LTx) with most patients reaching baseline (highest) function by 1 year. Patients with BLAD (defined as attaining <80% predicted baseline FEV1 and FVC) have increased mortality (Liu, J., et al. J Heart Lung Transplant 2018; 37:895-902). Our aim is to determine whether lung function measurements within 3 months post-LTx can accurately predict BLAD.
Methods: 207 double-LTx patients enrolled from December 2017 with at least 1 year of follow-up and paired oscillometry-spirometry data were included. Spirometry and oscillometry measurements at the first visit and at 3 months post-LTx were assessed using forward step-selection and model performance was internally validated using repeated k-fold cross validation. Demographic and perioperative parameters were included as candidate predictors.
Results: BLAD patients (n=104) differed from patients who achieved normal baseline lung function (n=103) in initial and 3-month lung function metrics, underlying lung disease, duration of intubation, and recipient age. Of the models tested, the percent predicted FEV1 (%FEV1) at 3-months post-LTx alone is the strongest predictor of BLAD (apparent AUC: 0.924, 95% CI 0.888-0.959, validated AUC: 0.924, 95% CI 0.905-0.943). The odds ratio for this parameter is 0.056, indicating that a patient with a 3-month %FEV1 1- standard deviation below the mean of our dataset is 17.8 (95% CI: 8.93-41.2) times more likely to develop BLAD.
Conclusion: %FEV1 at 3 months post-transplant is an excellent predictor of BLAD status. An early marker of BLAD will allow for appropriate allocation of care to facilitate interventions, to improve survival."
Supported by: Division of Respirology, Department of Medicine, University of Toronto.

Abstract #15

Investigation of pleural cavity B cells in a minor alloantigen-mismatched mouse orthotopic lung transplant model

Sumiha Karunagaran (1, 3), Jillian Oliver (1), Tereza Martinu (1, 2), Stephen Juvet (1, 2, 3)

sumiha.karunagaran@uhnresearch.ca

1. Latner Thoracic Surgery Research Laboratories, Toronto General Research Institute, University Health Network.
2. Division of Respirology, Department of Medicine, University of Toronto.
3. Department of Laboratory Medicine and Pathobiology, University of Toronto.

Introduction & Objectives: We previously showed that recipient B cells are necessary for the development of chronic allograft fibrosis after ischemia-reperfusion injury (IRI) in a C57BL/10 (B10, H-2b)-to-C57BL/6 (B6, H-2b) minor alloantigen-mismatched mouse orthotopic lung transplant (OLT) model. The observed IRI-augmented chronic rejection mimics restrictive allograft syndrome (RAS)-like pathology in humans, with extensive parenchymal and pleural fibrosis. CD5+ CD11b- B1 B cells are known to reside and self-renew in the pleural cavity. We, therefore, hypothesized that pleural cavity B cells might contribute to IRI-augmented chronic lung allograft rejection in mice.
Methods: We performed B10-B6 OLT with either prolonged (6h at 4°C followed by 45 min at 37°C and 15min anastomosis time) or minimal (1h at 4°C followed by 15min anastomosis time) antecedent storage (Fig 1A). Necropsies were performed at day 28. B cells in lung allografts and pleural lavage (2mL saline injected into pleural space) were characterized using flow cytometry. Histopathology of lung allografts were evaluated in a blinded manner using an established scoring system.
Results: Parenchymal and pleural fibrosis (Fig 1B) were increased, although non-significantly, in prolonged storage (long OLT) group (Fig 1C). B cells (CD19+) were significantly decreased in the recipient pleural cavity post-OLT ($p<0.0001$) (Fig 1D). Proportions of CD5+ CD11b- B1 B cells (Fig 1E) tended to be higher in allografts displaying greater pathology (Fig 1F). The number of CD5+ CD11b- B1 B cells in the allograft was associated with parenchymal fibrosis ($R2=0.5215$, $p=0.0024$) (Fig 1G).
Conclusion: Our results suggest that CD5+ CD11b- B1 B cells may participate in RAS-like pathology in this model. Further work is needed to determine whether lung allograft CD5+ CD11b- B cells originate from the pleural cavity and to demonstrate a mechanistic role for these cells in chronic lung allograft fibrosis.

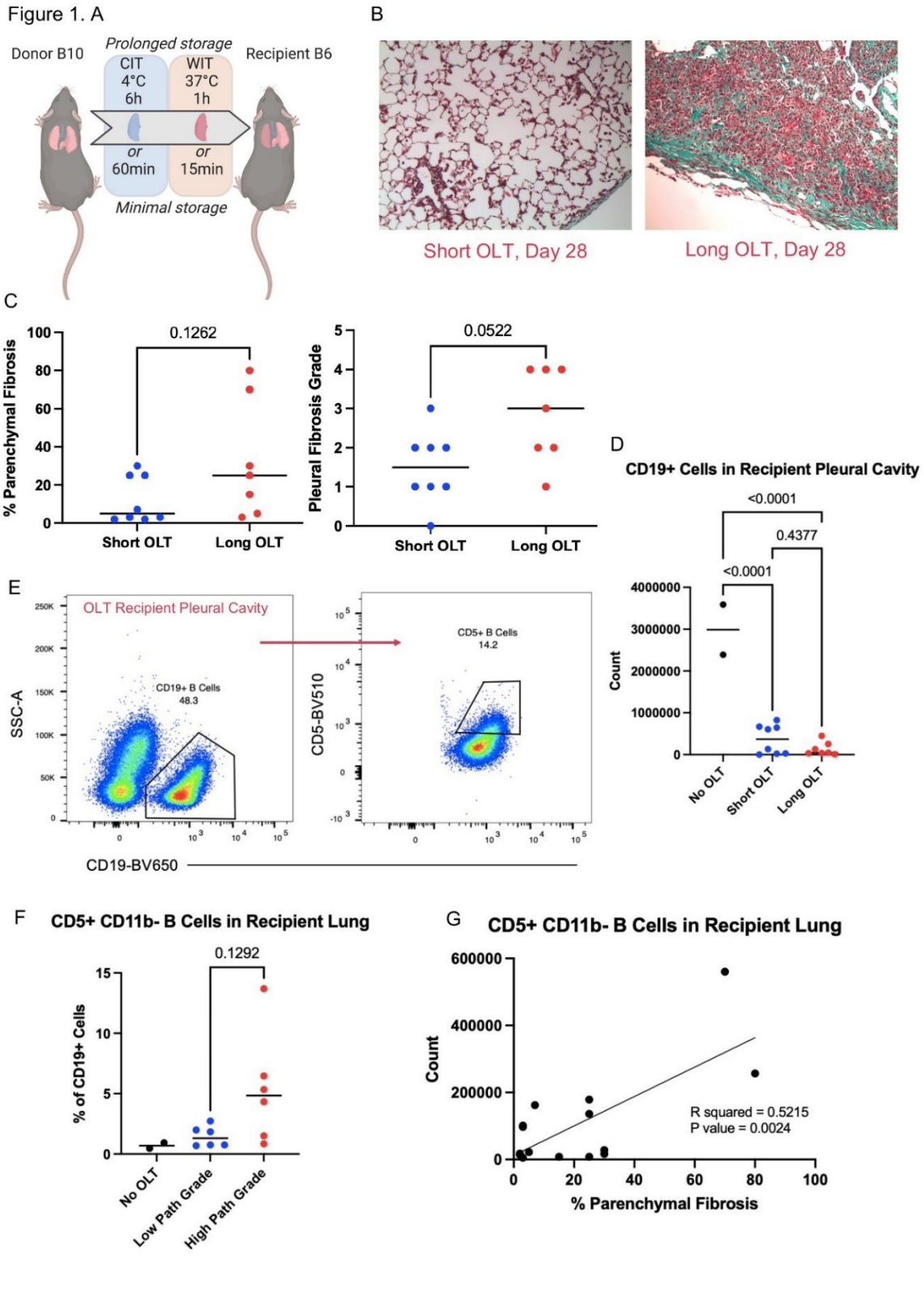


Figure 1. A
Donor B10
Prolonged storage
CIT
4°C
6h
or
60min
WIT
37°C
1h
or
15min
Minimal storage
Recipient B6
B
Short OLT, Day 28
Long OLT, Day 28
C
% Parenchymal Fibrosis
0.1262
Short OLT
Long OLT
Pleural Fibrosis Grade
0.0522
Short OLT
Long OLT
D
CD19+ Cells in Recipient Pleural Cavity
<0.0001
0.4377
<0.0001
Count
No OLT
Short OLT
Long OLT
E
OLT Recipient Pleural Cavity
SSC-A
CD19+ B Cells
48.3
CD19-BV650
CD5+ B Cells
14.2
CD5-BV510
F
CD5+ CD11b- B Cells in Recipient Lung
0.1292
% of CD19+ Cells
No OLT
Low Path Grade
High Path Grade
G
CD5+ CD11b- B Cells in Recipient Lung
Count
R squared = 0.5215
P value = 0.0024
% Parenchymal Fibrosis

Abstract #16

Effects of implementing GLI-2012 reference equations on pulmonary function test (PFT) interpretations

Haruna Kitazawa (1), Annie Jiang (1), Joyce K.Y. Wu (1,2), Cynthia Nohra (1), Honami Ota (1), Clodagh Ryan (1,2), Chung-Wai Chow (1,2)
Haruna Kitazawa haruna.kitazawa@uhnresearch.ca

1. Division of Respirology, Department of Medicine, University of Toronto.
2. Toronto General Hospital Pulmonary Function Laboratory, University Health Network

Introduction: Race/ethnicity are important features in determination of normal reference values according to the Global Lung Function Initiative (GLI-2012) guidelines. The PFT laboratories in our center use the Canadian reference equations derived from a healthy Caucasian cohort (Gutierrez C, et al. Can Respir J, 2014). The appropriateness of applying the Canadian reference equations to the multi-ethnic population in Canada has not been assessed.
Objectives: To evaluate the effects of changing from the Canadian reference equations to GLI-2012 equations on PFT interpretation in a multiethnic population, and to identify ethnic groups where discrepant interpretation are common.
Methods: We applied the Canadian, GLI-ethnic-based (GLI-Race), and GLI- ethnic-neutral (GLI-Other) reference equations to PFT data from 406 patients (aged 20-80 years) between 2017-2021. We compared concordance of abnormal diagnoses (FVC, FEV1, and FEV1/FVC < LLN) amongst the 3 reference sets and evaluated whether race/ethnicity was associated with discordance.
Results: Of 406 participants, 43.6% were non-Caucasian. The Canadian reference equations led to higher rates of abnormal (<LLN) FVC and FEV1 compared to GLI-Race and GLI-Other in all groups. The discordance was highest when comparing the Canadian reference equations to GLI-Race interpretations in Black, South East Asian, and Mixed/other ethnic groups. In contrast, the frequency of discordance did not differ among ethnic groups when the Canadian reference equations were compared with GLI-Other. There was high concordance in FEV1/FVC interpretation amongst the 3 reference equations.
Conclusion: Interpretation using the Canadian reference equations was associated with overdiagnosis of restrictive defects in some race/ethnicity groups compared to GLI-Race.
We thank all participants, Chow Research Group members, and the TGH PFT Laboratory. This work was supported by the Lung Health Foundation, , CIHR, and Natural Sciences and Engineering Research Council Collaborative Health Research Programme H. Kitazawa is supported by the scholarship funded by the Nakayama Foundation for Human Science and Ibaraki prefecture/ International Medical Center, University of Tsukuba hospital.

Abstract #17

Deep Learning Using Multi-Layer Perceptron Improves the Diagnostic Acumen of Spirometry

Amanda Mac (1), Tong Xu (1), Joyce Wu (2), Clodagh Ryan (1, 2), Shahrokh Valaee (3), Chung-Wai Chow (1, 2)

amanda.mac@uhnresearch.ca

1. Division of Respirology, Department of Medicine, Temerty Faculty of Medicine, University of Toronto.
2. Pulmonary Function Laboratory, Toronto General Hospital, University Health Network.
3. Department of Electrical & Computer Engineering, Faculty of Applied Sciences and Engineering, University of Toronto.

Introduction/Objectives: Spirometry and plethysmography are the clinical gold standard pulmonary function tests (PFT) for diagnosis and management of lung disease. Due to the inaccessibility of plethysmography, spirometry is often used alone, but this can lead to missed or misdiagnoses as spirometry cannot identify restrictive nor early obstructive disease without plethysmography. We propose that a deep learning model using multi-layer perceptron (MLP) can differentiate normal, obstructive, restrictive, and mixed obstructive-restrictive defects based on spirometry. We hypothesize MLP can improve the diagnostic acumen of spirometry, eliminating the need for plethysmography.
Methods: Full PFTs from 748 patients, labelled according to international guidelines, were used. We built the MLP model using 2582 PFTs from the first 477 patients, randomly divided into training (80%), validation (10%) and test (10%) sets. The model was then validated using the first 477 patients for training, and 1245 PFTs from the next 271 patients for validation (136 patients) and test (135 patients) sets. MLP classified lung conditions based on different combinations of inputs: (1) spirometry (FVC, FEV1, FEF25-75), plethysmography (TLC, RV) and biometrics (sex, age, height); (2) spirometry and biometrics; (3) spirometry and plethysmography; (4) spirometry. 10 experiments were completed for each combination of input parameters.
Results: Accuracies from the first 477 patients were similar when inputs included biometrics, spirometry and plethysmography (95±3%) vs. biometrics and spirometry (90±2%). Validation with data from the next 271 patients confirmed similarly high accuracies for biometrics, spirometry and plethysmography (95±2%) vs. biometrics and spirometry only (95±2%). Removal of biometrics reduced accuracies to 63±7% for spirometry and plethysmography, and 56±9% for spirometry.
Conclusion: MLP with spirometry alone was able to classify lung conditions with 95% accuracy. Deep learning using biometric and spirometric measures (FVC, FEV1, FEF25-75) can provide diagnostic sensitivities that are comparable to full PFTs, improving diagnostic acumen when only spirometry is available.
The study is supported by a grant-in-aid from the Lung Health Foundation, the Pettit Block Term Grants, the CIHR/NSERC Collaborative Health Research Program (grant #415013) and the Ajmera Foundation Multi-Organ Transplant Innovation Fund. A.M. was supported by an Amgen Scholarship. We thank the Registered Pulmonary Technologists at Toronto General Hospital for

helping to conduct the study, members of Dr. Chung-Wai Chow's laboratory for collecting and maintaining the research data, and the 2019 University of Toronto PFT Committee for their work on developing the University of Toronto Guidelines for PFT Interpretation, 8th Edition.

Abstract #18

Transcriptomic profiling of small airway epithelium club cells in chronic lung allograft dysfunction

Olivia Mekhael (1, 2), Allen Duong (1), Benjamin Renaud-Picard (1), Tina Daigneault (1), Ankita Burman (1), Sajad Moshkelgosha (1), Aaron Wong (1), Mingyao Liu (1), Stephen C Juvet (1, 2), Tereza Martinu (1, 2)

olivia.mekhael@uhnresearch.ca

1. Toronto Lung Transplant Program, Ajmera Transplant Centre, Toronto General Hospital Research Institute, University Health Network, Toronto.
2. Faculty of Medicine, University of Toronto.

Introduction. The major barrier to long-term survival following lung transplantation is progressive scarring, termed chronic lung allograft dysfunction (CLAD). Two main phenotypes of CLAD have been identified: bronchiolitis obliterans syndrome (BOS) characterized by obliterative bronchiolitis fibrosis and inflammation of small airways; and restrictive allograft syndrome (RAS) defined by pleural and parenchymal fibrosis. Ongoing rejection mediated by alloimmune responses along with repeated injuries and loss of epithelial club cells are hallmarks of CLAD pathogenesis. Club cells are thought to have protective and anti-inflammatory roles. We hypothesize that CLAD is associated with an aberrant transcriptomic profile in club cells related to differential cell death, proliferation, and senescence gene expression.
Methods. We used single cell RNA sequencing (scRNAseq) to establish transcriptomic signatures of allograft airway club cells in single cell suspensions generated from lung allografts affected by CLAD (6 BOS, 3 RAS), explanted during autopsy or lung retransplant surgery, and from control donor lung samples (n=5). The scRNAseq dataset was processed, explored, and visualised using Cellenics® community instance hosted by Biomage.
Results. Our findings show profound loss of epithelial cells, including club cells, in RAS compared to BOS and controls (Fig. 1A). Further, genes related to I) extrinsic apoptosis (TNFSF10), II) intrinsic apoptosis (BAG1, BIK), III) autophagy (ATP1B1, PRKAA2), IV) mucin, and V) growth factors were preferentially/relatively upregulated in BOS and RAS club cells compared to control club cells. VI) Proliferation-related gene (MCM2) was downregulated and VII) senescence-related genes (CDKN2A, CDKN1A) were upregulated in RAS club cells compared to BOS and control club cells (Fig. 1B).
Conclusion. Our data show a disruption of the transcriptomic profile of club cells found in lung transplant recipients affected by CLAD, especially RAS, suggesting increased cell death and senescence processes and reduced proliferation compared to controls. Thus, this study provides insight into potential mechanisms underlying CLAD.
This research is supported by the University of Toronto, Division of Respirology, CME Fellowship Award (to OM), a Sanofi Research Award (to TM and SCJ), and the Cystic Fibrosis Foundation Research Award (to TM).

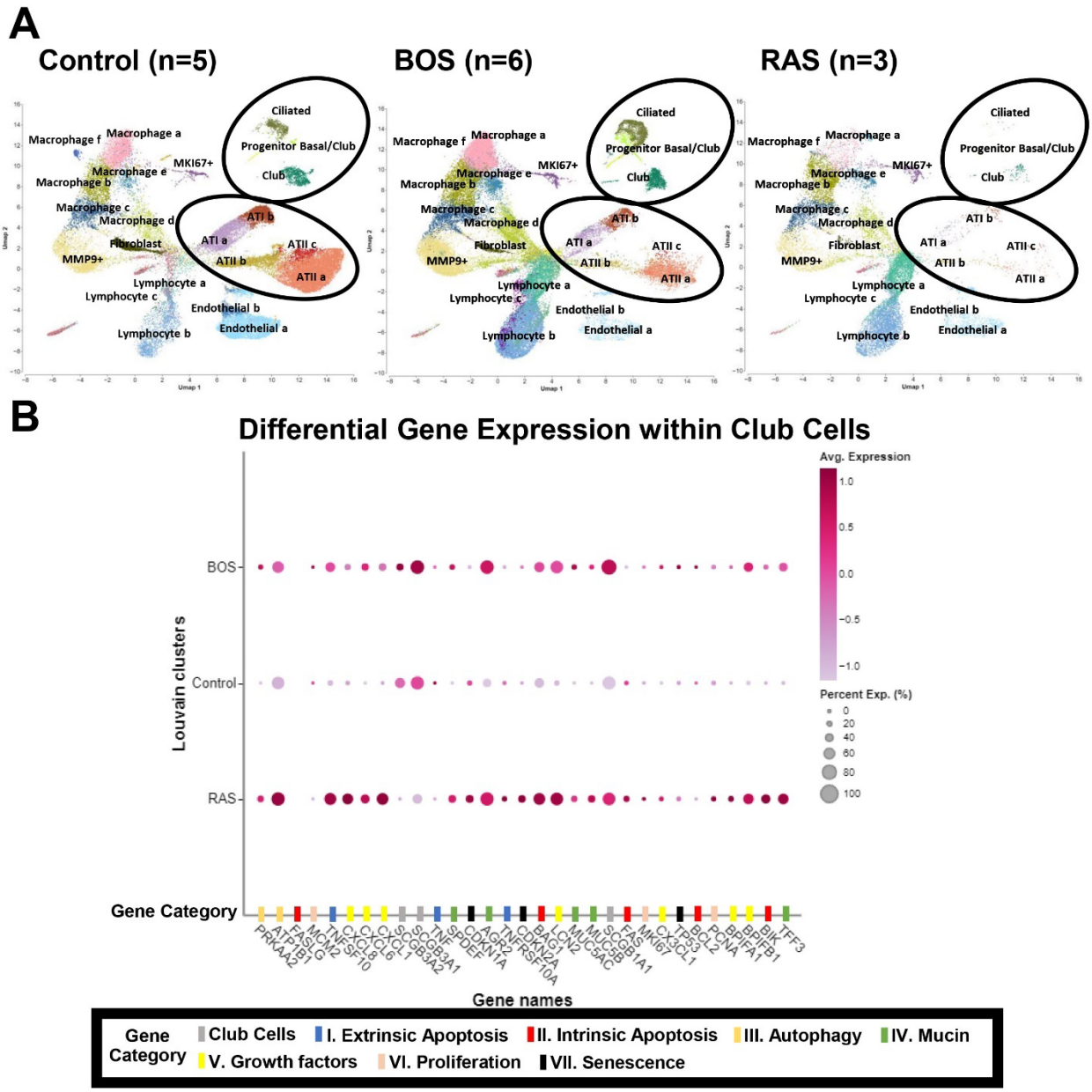


Figure 1. Small Airway Epithelium Club Cells-focused scRNAseq Analysis of Regulated Cell Death, Proliferation, Senescence, Mucin, and Growth Factors-related Genes in BOS vs. RAS vs. Control Cases. (A) Single cell suspensions were generated from lung allografts affected by CLAD, explanted during autopsy or lung retransplant surgery. Samples were submitted for scRNAseq processing and sequencing. An integration analysis of six BOS, three RAS, and five control donor lung samples was conducted. **(B)** Dot plots showing regulated cell death [extrinsic apoptosis *(TNF, TNFSF10, TNFRSF10A)*, intrinsic apoptosis *(FAS, FASLG, BAG1, BIK, BCL2)*, autophagy *(ATP1B1, PRKAA2)*], proliferation *(MKI67, PCNA, MCM2)*, and senescence *(TP53, CDKN2A, CDKN1A)*-related transcripts, mucin-related transcripts, and growth factors assessed in club cells *(SCGB1A1, SCGB3A1, SCGB3A2)* found in BOS, RAS, or controls. To note, mucin-related genes and growth factors were selected based on findings by "Zuo W-L, Rostami MR, LeBlanc M, Kaner RJ, O'Beirne SL, Mezey JG, *et al.* (2020). Dysregulation of club cell biology in idiopathic pulmonary fibrosis. *PLoS ONE* 15(9): e0237529". The scRNAseq dataset was processed, explored, and visualised using Cellenics® community instance (https://scp.biomage.net/) hosted by Biomage (https://biomage.net/).

"This research is supported by the University of Toronto, Division of Respirology, CME Fellowship Award (to OM), a Sanofi Research Award (to TM and SCJ), and the Cystic Fibrosis Foundation Research Award (to TM)".

Abstract #19

Evaluation of Frailty in Patients with Pulmonary Hypertension

Rozhan Momen (1, 2), Daniel Santa Mina (1, 2), Noor Al Kaabi (2,3), Sahar Norouzpour (2), Fatemeh Zaeimi (2, 4), Anna Beale (2, 5), Shahidehalsadat Safavi (2, 5), Nadia Sharif (2, 5), Lianne Singer (2, 7), Jakov Moric (5), Marc De Perrot (4, 6), Laura Donahoe (4, 6), John Granton (5, 6), Dmitry Rozenberg (2, 4, 7).

Rozhan Momen rozhan.momen@uhnresearch.ca

1. Faculty of Kinesiology and Physical Education, University of Toronto.
2. Toronto General Hospital Research Institute, University Health Network, Toronto.
3. Institute of Medical Science, University of Toronto.
4. Thoracic Surgery and CTEPH program, UHN, Toronto.
5. Division of Respirology Pulmonary Hypertension program, UHN, Toronto.
6. Temerty Faculty of Medicine, University of Toronto, Toronto.
7. Respirology and lung Transplant Program, UHN, Toronto.

Introduction & Objectives: Pulmonary Hypertension (PH) is a progressive vascular condition characterized by increased morbidity and mortality. Identification of modifiable risk factors such as frailty, a biological syndrome characterized by decreased physiological reserve, may have important implications on pharmacological management and prognosis as shown in other chronic lung conditions. However, frailty in PH has not been previously evaluated. This project aims to; (1) Evaluate the prevalence of frailty in PH patients and (2) Compare Health Related Quality of Life (HRQoL), physical function and disease severity measures between frail and non-frail patients.
Methods: Prospective, cross-sectional study targeting 90 adult patients with a clinical diagnosis of pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension (CTEPH) recruited from outpatient clinics at Toronto General Hospital. Frailty was defined in accordance to Fried Frailty Index ≥ 3 based on accepted parameters of shrinking, weakness, exhaustion, low activity and slowness. A combination of patient reported outcome measures (Short-form 36, emphasis-10) and functional assessments (6-minute walk test and Short Performance Physical Battery (SPPB)) were undertaken. T-tests were used to assess differences between frailty groups with respect to HRQoL and functional measures.
Results: 32 participants (54±16 years, 73% female, 28.2± 7.3 kg/m2) completed assessments. 7 (22%) participants were deemed frail based on the Fried index. Frail PH patients were observed to have worse HRQoL than non-frail patients in emPHasis-10 (34 vs. 28.5) and SF-36 Physical Component Score (25.1 vs. 32.8), $p < 0.05$ for both comparisons. There was no difference observed in SPPB (frail: 8 [6.5-9] vs. non-frail: 9.5 [7-11], p=0.17) or 6-minute walk distance (frail: 430 IQR [336-442] vs. non-frail: 416 [349-483] meters, p= 0.23).
Conclusions: Preliminary findings demonstrate frailty affects over one-fifth of PH patients. Frailty is associated with lower generic and PH specific HRQoL with a trend towards impairments in lower extremity physical performance. Study is ongoing exploring other frailty constructs and mechanisms of skeletal muscle structure and function.

Funded by Canada Graduate Scholarship-Masters (CGS-M) and Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine.

Abstract #20

Pulmonary Rehabilitation in Lung Transplant Candidates with Pulmonary Arterial Hypertension

Maha Munawar (1), Lisa Wickerson (2, 3), Sahar Nourouzpour (3), Marc de Perrot (1, 4), John Granton (1, 5), Dmitry Rozenberg (1, 3, 6)

maha.munawar@mail.utoronto.ca

1. Temerty Faculty of Medicine, University of Toronto.
2. Physical Therapy, University of Toronto.
3. Toronto General Hospital Research Institute, University Health Network.
4. Thoracic Surgery and CTEPH program, University Health Network.
5. Division of Respirology, Pulmonary Hypertension program, University Health Network.
6. Respirology and Lung Transplantation program, University Health Network.

INTRODUCTION: Lung transplant programs often mandate participation in pulmonary rehabilitation (PR) as exercise capacity has been shown to be a major predictor of post-transplant outcomes. Lung transplant candidates with pulmonary arterial hypertension (PAH) face a substantial symptom burden and progressive functional decline despite medical management. The response to PR has not been well characterized in PAH and traditionally this group has been excluded from PR studies.
OBJECTIVES: 1) Characterize the PAH population and their ability to participate in outpatient PR pre-transplant 2) Assess the response of exercise capacity with pre-transplant PR.
METHODS: Single-centre retrospective cohort study of adult PAH lung transplant candidates listed between January 1, 2014 to December 31, 2018. Participants attended facility-based outpatient PR three times per week focusing on aerobic, strength and flexibility exercises. Functional capacity was measured using the 6-minute walk distance (6MWD) at listing, 4-6 weeks, and at 3-month intervals until transplantation. Wilcoxon signed-rank test was used to assess changes in 6MWD.
RESULTS: 48 PAH patients were included (age 49 ± 12 years, 67% females, and BMI 25 ± 5 kg/m2). Baseline mean pulmonary artery pressure (mPAP) was 54 ± 16 mmHg. 6 died pre-transplant and 2 were medically delisted. Of the 40 patients that survived to transplantation, 15 patients (37.5%) were admitted with decompensated right heart failure pre-transplant and 11 patients (27.5%) required bridging to transplantation. Compared to a mean listing 6MWD of 329 ± 112 metres, the final 6MWD pre-transplant improved by 35 ± 100 metres (n=25, p=0.06). One patient required PAH therapy adjustment to enhance PR participation.
CONCLUSION: Transplant candidates with PAH are severely ill with frequent hospital admissions and bridging to transplantation required in more than a quarter of patients. For those able to participate in outpatient PR, a modest gain in exercise capacity was demonstrated. Inpatient rehabilitation strategies are an important consideration in this patient population given the high proportion admitted to hospital.
Department of Medicine at University of Toronto and funding support from Sandra Faire and Ivan Fecan Professorship in Rehabilitation.

Abstract #21

Unnecessary inhaler use in interstitial lung disease: a needs assessment

Stephanie Nevison (1), Shane Shapera (1, 2), Jolene Fisher (1, 2), Lee Fidler (1, 2, 3)

stephanie.nevison@mail.utoronto.ca

1. Department of Medicine, University of Toronto.
2. Toronto General Hospital, University of Toronto.
3. Sunnybrook Health Sciences Centre, University of Toronto

Introduction & Objectives: Interstitial lung disease (ILD) patients may be inappropriately prescribed inhalers without an indication, as symptoms of ILD can overlap with chronic airways disease. Unnecessary inhaler use could contribute to avoidable side effects, costs, and environmental impact. The purpose of this study was to quantify the extent of unnecessary inhaler use in patients with ILD.
Methods: Patients from the ILD clinic at Toronto General Hospital were reviewed over a six-month period. Visit type (new consultation or follow-up) and patient diagnosis were documented. Appropriate indications for chronic inhaler use included: airflow obstruction on pulmonary function testing (PFT), bronchodilator response, reported history of asthma, smoking history greater than 15 pack/years, emphysema on CT chest imaging and/or reported benefit from therapy. If the patient had no indication, we documented whether recommendations to discontinue inhalers were suggested.
Results: In total, 191 ILD patients comprising new and follow-up visits were reviewed. Of these, 48 (25.1%) were taking inhaled medications, with 17 (8.9%) being new referrals and 31 (16.2%) seen for follow-up visits. No indication could be identified for inhaler use in 15 (31.3%) patients. There was no significant difference between the proportion of new and follow-up patients taking inhalers without an indication (7 (41.2%) vs. 8 (25.8%) respectively, p=0.27). In those without an indication, the most prescribed inhalers were inhaled corticosteroid (either alone, or in combination with a long-acting beta agonist), taken by 10 (66.7%) patients. The most common indication for inhaler use was confirmed airflow obstruction on PFT, 17 (51.5%) patients. Even in the absence of an indication, no patients were advised to discontinue inhaler treatment.
Conclusion: A minority of ILD patients are prescribed inhalers, however nearly one-third of patients on inhalers do not have an indication for their use. The creation of inhaler deprescribing criteria and reminder interventions could serve to reduce unnecessary inhaler use, costs, and environmental impact.
Supported by: Division of Respirology, Department of Medicine, University of Toronto.

Abstract #22

Characterizing Respiratory Mechanics in Lymphangioleiomyomatosis as Measured by Oscillometry and CT Imaging

Cynthia Nohra (1), Joyce K. Y. Wu (1), Anastasiia Vasileva (1), John Thenganatt (1), Clodagh Ryan (1), Michael McInnis (1), Zoltan Hantos (2), Chung-Wai Chow (1)

cynthia.nohra@mail.utoronto.ca

1. University Health Network, University of Toronto.
2. Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary.

Introduction: Lymphangioleiomyomatosis (LAM) is a rare lung disease that presents with cysts on chest imaging and progressive pulmonary function impairment. LAM patients are reported to have 3-4-fold decrease in small airways compared to healthy subjects. While spirometry is used to monitor LAM, it is known to be poorly sensitive to small airways. Oscillometry (Osc), a new PFT modality, identifies measures sensitive to changes in the small airways. Quantitative analysis of high-resolution chest tomography (CT) is increasingly used in different diseases as markers of severity.
Objective: To characterize Osc and quantitative CT measurements in LAM patients.
Methods: All LAM patients followed at our center were enrolled for Osc prior to routine PFTs from Aug 2020 onward. CTs done within 6 months of the PFT/Osc were used for lung density and volume analysis.
Results: Of 35 LAM patients (age=48.8±12.5 yrs;34F,1M), 12 had Sporadic (S-LAM), 11 had Tuberous Sclerosis Complex (TSC-LAM) and 12 had unknown LAM (NYD-LAM). Spirometry and plethysmograph-derived total lung capacity (TLC) were normal and similar amongst 3 groups (mean ± SD: %FEV1=76.6±21.8, %FVC=90.1±16, %TLC=99.3±11.2). However, Osc indicated ventilatory inhomogeneity with mildly elevated AX (area of reactance, >8.0 cmH2O/L) in all groups. Higher AX reflects smaller lung volumes in communication with ventilation. CT-derived highest lung attenuation area (LAA) relative to TLC, a metric of cystic disease burden, was highest in NYD-LAM.
Conclusion: These data suggest that Osc and quantitative CT may provide additional information about subtle physiologic abnormalities in LAM patients that are not apparent with PFTs alone.

Abstract #23

Lung Function Monitoring in Patients with Pulmonary Graft vs Host Disease Following Bone Marrow Transplantation (BMT) using Oscillometry

Honami Ota (1), Cynthia Nohra (1), Joyce K. Y. Wu (1, 2), Qian Huang (1), Lauren Day (1), Zoltan Hantos (3), Jeff Lipton (4), Clodagh Ryan (1), Chung-Wai Chow (1)

honami.ota@uhnresearch.ca

1. Division of Respirology, University Health Network (UHN), Toronto.
2. Toronto General Hospital Pulmonary Function Laboratory, University Health Network.
3. Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary
4. Hans Messner Allogeneic Blood and Marrow Transplantation Program. Princess Margaret Cancer Centre, University Health Network (UHN).

Background: Pulmonary graft versus host disease (pGvHD) is a significant cause of morbidity and mortality post bone marrow transplant (BMT). The histological changes of pGvHD are primarily in the small airways, an area of the lung not well evaluated by spirometry and conventional pulmonary function tests (PFT). Respiratory oscillometry (OSc) is a different PFT modality that is highly sensitive to changes in the smaller airways. We hypothesize that OSc can detect changes in respiratory mechanics associated with pGvHD that may not be detectable by conventional PFTs. The aim of this study is to investigate the utility of OSc in identifying changes in lung mechanics in pGvHD.
Method: From September 2017 onwards, patients undergoing BMT were prospectively enrolled for paired OSc and PFT testing before and at 2, 4, 6, 9, 12, 18, and 24 months following BMT. OSc and PFT were conducted in accordance with international guidelines. The tremoflo device was used in our study. The 2014 NIH chronic GVHD diagnostic criteria were used to diagnose pGvHD.
Results: Of 312 recruited Pre-BMT patients (62F: 75M, mean age = 55.23 yrs, range 18.3 to 77.9), 268 underwent BMT and 137 were actively followed post-BMT at UHN up until February 28, 2021. Mean follow-up was 12 months (range, 1-27). Eight of the 137 subjects had developed pGvHD (mean time=8.25 months, range 2-18 months post-BMT). Patients who developed pGvHD were similar to pGvHD-free patients with respect to demographics, underlying diagnoses, and smoking history. Conventional PFT showed <10% in FEV1 (mean decline of 7.49%) at time of pGvHD diagnosis. We also observed no evidence of gas trapping as measured by RV/TLC ratio. In contrast, OSc metrics of ventilatory inhomogeneity, particularly, AX (area of reactance), X5 (reactance at 5 Hz) and R5-19 (frequency dependence of resistance, a key metric of small airway obstruction), all worsened at time of pGvHD diagnosis. All exhibited a >15% change compared to baseline. AX, X5, and R5-19 exhibited more than 36%, 21%, and 17% change respectively.
Conclusion: Longitudinal follow-up in this cohort of BMT patients revealed a pGvHD of 6%. Conventional PFT did not show significant changes at time of pGvHD diagnosis. However, Osc and the metrics of R5-R19, X5, and AX were worse at the time of pGvHD diagnosis compared to baseline values. These observations suggest that OSc is more sensitive to the changes in lung mechanics than spirometry following BMT.

Abstract #24

Impact of cognitive capacity on physical performance in chronic obstructive pulmonary disease patients: a scoping review

Peter Rassam (1, 2), Eli Maria Pazzianotto-Forti (2), Umi Matsumura (3), Ani Orchanian-Cheff (4), Antenor Rodrigues (5), Daniel Langer (6), Dmitry Rozenberg (7), W. Darlene Reid (2)

peter.rassam@mail.utoronto.ca

1. Rehabilitation Sciences Institute, School of Graduate Studies, University of Toronto.
2. Department of Physical Therapy, University of Toronto.
3. Department of Health Sciences, Graduate School of Biomedical Sciences, Nagasaki University.
4. Library and Information Services, University Health Network.
5. Department of Critical Care, St. Michael's Hospital.
6. Department of Rehabilitation Sciences, KU Leuven.
7. Department of Medicine, Respirology, University Health Network.

Introduction & Objectives: Chronic obstructive pulmonary disease (COPD) is often accompanied by impaired cognitive and physical function. However, their interrelationship is not well studied. The aim of the review was to determine the impact of cognition on physical performance in COPD.
Methods: Established scoping review methods were performed including searches of the databases: MEDLINE, EMBASE, Cochrane Systematic Reviews, Cochrane (CENTRAL), APA PsycINFO, and CINAHL. Search terms included: COPD, cognition, and exercise capacity. Two reviewers independently assessed articles for inclusion, data abstraction, and quality assessment.
Results: Of 11,252 identified articles, 44 met the inclusion criteria. The study included 5,743 individuals with COPD (68% male) with the forced expiratory volume in one second range of 24—69% predicted. Cognitive scores correlated with strength, balance, and hand dexterity, while 6-minute walk distance (n=9) was usually similar among COPD patients with and without cognitive impairment. In 2 reports, regression analyses showed that delayed recall and the trail making test were associated with balance and handgrip strength, respectively. Dual task studies (n=5) reported impaired balance or gait in COPD patients compared to healthy adults. Cognitive or physical Interventions (n=20) showed variable improvements in cognition and exercise capacity.
Conclusion: Cognition in COPD appears to be more related to balance, hand, and dual task function, than exercise capacity.

Abstract #25

Respiratory and locomotor rhythmic activities associated to a tachykinin precursor 1 medullary circuit

Jean-Philippe Rousseau (1), Carolina da Silveira Scarpellini (1), Gaspard Montandon (1,2)

jean-philippe.rousseau@unityhealth.to

1. St. Michael's Hospital, Unity Health Toronto.
2. Division of Respirology, Department of Medicine, University of Toronto

Introduction & Objective: The respiratory central pattern generator (CPG) is a complex organization of neural circuits within the brainstem generating independently a rhythmic breathing pattern and synchronizing its activity with other communicating networks like the locomotor CPG. At the core of this breathing CPG, we find the preBötzinger Complex (preBötC), a medullary aggregation of neurons composed of various excitatory and inhibitory subpopulation. Here we aimed to further characterize the subpopulation of glutamatergic neurons expressing the tachykinin precursor 1 (tac1) as they potentially modulate respiratory rhythmogenesis and might interact with locomotion.
Methods: Using a Cre-loxP recombination approach, we injected in Tac1 Cre recombinase mice the adeno-associated virus containing the gene cassette of the excitatory channelrhodopsin-2 ChETA flanked between loxP sites. A 200 µm optical fiber was then fixed above the preBötC for laser stimulation with blue light (wavelength: 480 nm) in freely behaving animals. After four weeks, the mouse was placed in a plethysmographic chamber and breathing was measured while laser stimulations (40 Hz) were performed under baseline conditions. Using a high-definition camera placed at the bottom of the box, mouse movements were tracked and analyzed in parallel with breathing.
Results: Laser stimulation of preBötC tac1-expressing neurons increases respiratory rate in a state dependent manner in freely moving/awake animals and increases velocity (cm/s), positively correlated with the breathing response.
Conclusion: Our study provides important insights into the internal organization of the preBötC and portrays a more complete phenotype of the tac1-expressing neurons located in this region and how they might affect rhythmic activities.
Supported by: Canadian Institutes of Health Research (CIHR), Fonds de Recherche du Québec – Santé (FRQS)

Abstract #26

Evaluation of Frailty in Patients Admitted with Exacerbations of Chronic Obstructive Pulmonary Disease

Kimia Sheikholeslami (1), Sahar Nourouzpour (2), Matthew B Stanbrook (2), Kirsten Wentlandt (3), Robert Wu (1), W Darlene Reid (4), Dmitry Rozenberg (2)

kimia.sheikholeslami2@uhn.ca

1. Temerty Faculty of Medicine, Internal Medicine, University of Toronto.
2. Division of Respirology, University Health Network, Temerty Faculty of Medicine, University of Toronto.
3. Division of Palliative Care, University Health Network, Toronto.
4. Department of Physical Therapy, University of Toronto.

Introduction and Objectives: Acute exacerbation of COPD (AECOPD) are the leading cause of hospitalizations in Canada. Recognition of frailty in COPD inpatients may lead to earlier initiation of interventions to improve outcomes, which may help hasten recovery. However, frailty and its clinical implications during AECOPD have not been well described. We aim to evaluate the difference in hospital length of stay (LOS), readmissions and one-year mortality between frail and non-frail COPD patients.
Methods: This is a retrospective cohort study of patients admitted with AECOPD to the University Health Network from January 1, 2017 to March 14, 2018. Patient demographics, comorbidities, and details surrounding the index hospitalization were abstracted from chart review. Frailty was measured using a cumulative deficits frailty score, which incorporates physical and psychosocial health elements. The frailty index was derived from the ratio of total deficits present with frailty defined as a frailty index ≥ 0.25, as accepted convention. The difference in hospital LOS, 1-year readmissions, and mortality were compared between frail and non-frail patients.
Results: 100 COPD patients (73 ± 10 years, 58% males, BMI of 26.4 ± 7.6 kg/m2, and FEV1 of 40 IQR [29-55]) % were included, of which 78% were deemed frail. The median hospital LOS was 4 IQR [2 to 7] days, with no difference between frail and non-frail patients (p=0.61). In the one-year following hospital admission, 33 (42%) frail patients were readmitted with AECOPD compared to 8 (36%) without frailty, p=0.69. Frail patients (9 (12%)) compared to non-frail (1 (0.5%)) had a greater 1-year mortality post-hospital discharge, but this was not statistically significant (p=0.33).
Conclusion: Frailty was prevalent in this cohort observed in over three-quarters of COPD patients There was no difference in AECOPD readmissions, but a signal towards increased one-year mortality was observed in the frailty group. The study is ongoing evaluating the functional recovery post AECOPD.
Supported by: Temerty Faculty of Medicine, University of Toronto and Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine. Supported by CIHR Project Grant (PJM: 179846).

Abstract #27

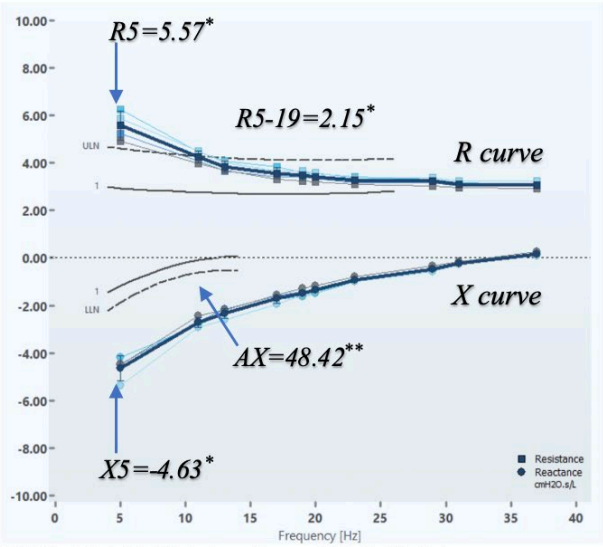
Characterization of chronic lung allograft dysfunction (CLAD) at time onset using respiratory oscillometry (Osc)

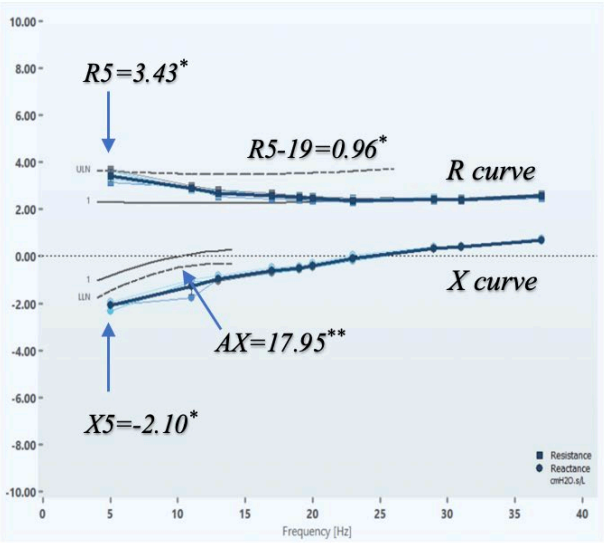
Anastasiia Vasileva (1), Nour Hanafi (1), Ella Huszti (4), Cynthia Nohra (1), Natalia Belousova (1), Joyce K. Y. Wu (1, 2), Clodagh Ryan (1, 2), Chung-Wai Chow (1, 3)

anastasiia.vasileva@uhnresearch.ca

1. Division of Respirology, Department of Medicine, Temerty Faculty of Medicine, University of Toronto
2. Pulmonary Function Laboratory, University Health Network
3. Toronto Lung Transplant Program, Ajmera Multi-Organ Transplant Unit, University Health Network
4. Biostatistics Research Unit, University Health Network

Introduction. CLAD, the leading cause of death post lung transplantation (LTx), is diagnosed based on persistent drop in FEV1. The two phenotypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), characterized by spirometry and chest imaging, have different prognoses. Osc is an effort-independent measure of pulmonary function more sensitive to small airway dysfunction.
Aim. To characterize Osc pattern at CLAD onset.
Methods. Of the 273/289 double LTx patients with paired Osc-spirometry and follow-up >6 months, 41/81 patients with CLAD had Osc at CLAD onset. Osc from 179 CLAD-free patients was time matched to each CLAD patient for comparison.
Results. CLAD and CLAD-free groups were significantly different in Osc measurement of resistance (R5=4.1 vs 3.5, R5-19=0.97 vs 0.55) and reactance (AX=18.1 vs 9.1, X5=-2.4 vs -1.6) ($p<0.05$). 31 CLAD cases were clearly identified as BOS (n=24; %TLC=78.0, FEV1/FVC=66.6) or RAS (n= 7; %TLC= 64.9, FEV1/FVC= 85.0). Osc was different between 2 groups with BOS characterized by high R5-19 (1.27 vs. 0.69), reactance (AX=20.9 vs 12.8) and oscillogram pattern characteristic of obstructive lung disease, whereas RAS resembled that of interstitial lung disease (Fig.1).
Conclusions. Osc at time of CLAD onset is different between RAS and BOS and could help phenotype CLAD without chest imaging when used with spirometry.





BOS: FLT-045; Test date: 2019-09-04 *RAS: FLT-127; Test date: 2019-12-16*

Figure 1. Oscillograms at time of CLAD onset. *Units of measurement: * cmH20.s/L; ** cmH20/L.*
R curve=resistance curve; X curve=reactance curve; X5=reactance at 5 Hz; AX=reactance area between 5 Hz and resonance frequency; R5=resistance at 5 Hz; R5-19=difference in resistance between 5 and 19 Hz.

Abstract #28

The Association of Comorbid Insomnia and Sleep Apnea with Health-Related Quality of Life in Children with Obesity

Lena Xiao (1, 2), Giorge Voutsas (1, 2), Clodagh M. Ryan (2, 3), Sherri Lynne Katz (4, 5, 6), Indra Narang (1, 2)

lena.xiao@sickkids.ca

1. Division of Respiratory Medicine, Department of Pediatrics, The Hospital for Sick Children.
2. University of Toronto.
3. Department of Respirology, Department of Medicine, Toronto General Hospital, University Health Network.
4. Division of Respiratory Medicine, Children's Hospital of Eastern Ontario.
5. University of Ottawa.
6. Children's Hospital of Eastern Ontario Research Institute.

Background: Obstructive sleep apnea (OSA) and insomnia are highly prevalent in children, but their co-occurrence and the impact of comorbid insomnia and OSA (COMISA) on health-related quality of life (HRQOL) is unknown in children. The primary objective was to describe the association of COMISA, isolated OSA, and isolated insomnia with HRQOL in children with obesity compared to neither insomnia nor OSA. The secondary objective was to evaluate the association between polysomnogram variables and insomnia symptoms.
Methods: This was a cross-sectional study of children with obesity at two tertiary care centres. Insomnia symptoms and HRQOL were measured with the Pittsburgh Sleep Quality Index and Pediatric Quality of Life Inventory (PedsQL) questionnaires, respectively. Multivariable regression models were created to evaluate associations between sleep disorders and HRQOL and between polysomnogram parameters and insomnia symptoms.
Results: There were 97 children (median age 15.0 years, median body mass index z-score 3.8, 44.3% females). Of these children, 26 (27%) had isolated OSA, 34 (35%) had isolated insomnia, 14 (14%) had COMISA and 23 (24%) had neither insomnia nor OSA. Isolated insomnia was independently associated with a decreased total PedsQL score by 14.4 (95% confidence interval 6.0-23.8; $p<0.001$). There was no association between isolated OSA or COMISA with HRQOL. There were no clinically relevant associations between polysomnogram parameters and insomnia.
Conclusions: Children with obesity reported lower HRQOL in the isolated insomnia subgroup compared to children with neither insomnia nor OSA. Children in the COMISA and isolated OSA subgroups did not report lower HRQOL compared to children with neither insomnia nor OSA. These findings suggest that HRQOL is not worse in children with obesity who have co-existing insomnia and OSA.

Abstract #29

Association of chronic proton pump inhibitor use in lung transplant recipients with long-term outcomes: a retrospective cohort study

Kevin Zhang (1), Rayoun Ramendra (1), Juan Fernandez-Castillo (1), Gregory Berra (1), Rasheed Ghany (1), Jussi Tikkanen (1), Lianne G Singer (1), Meghan Aversa (1), Ella Huszti (2), Shaf Keshavjee (1), Jonathan Yeung (1), Tereza Martinu (1)

cykevin.zhang@mail.utoronto.ca

1. Toronto Lung Transplant Program, University Health Network, Toronto.
2. Biostatistics Research Unit, University Health Network, Toronto.

Introduction & Objectives: Proton pump inhibitors (PPI) are widely prescribed for lung transplant recipients in the absence of proven PPI-indicated conditions, despite little evidence supporting this practice. Several adverse effects related to chronic PPI use have been reported in observational studies. We aimed to characterize chronic PPI use in lung transplant recipients and assess its association with long-term outcomes, specifically chronic lung allograft dysfunction (CLAD) and death/retransplant.
Methods: All adult lung transplant recipients transplanted between 1999-2018 who survived past 1-year post-transplant and had at least 4 pulmonary function tests were included. Patients were classified as on-PPI if there was a recorded prescription in the electronic medical record for dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole before 1-year post-transplant that continued after 1-year post-transplant. All other patients were classified as off-PPI. Cox proportional hazards models were used to determine the associations between PPI use and outcomes.
Results: Chronic PPI use increased drastically from 1999 to 2018. Compared to the on-PPI group, the off-PPI group was younger, had fewer re-transplants, and more transplants before 2010. In univariable analyses, PPI use was protective against CLAD (HR=0.76[0.62-0.94], p=0.01) and death/retransplant (HR=0.82[0.67-0.99], p=0.04). These associations were no longer significant after adjusting for age, sex, transplant type, transplant number, transplant era, primary disease, and CMV mismatch in multivariable analyses for CLAD (HR=0.87[0.70-1.08], p=0.20) and death/retransplant (HR=0.83[0.68-1.02], p=0.07).
Conclusion: Chronic PPI use after the first post-transplant year in lung transplant recipients was associated with a non-statistically significant benefit in death/retransplant, independent of potential confounders. As additional unknown confounders may exist, contemporary randomized studies are needed to provide higher levels of evidence. Nonetheless, it may be reasonable to re-evaluate the practice of widely prescribing long-term PPIs in lung transplant recipients lacking a clear indication.

Abstract #30

Comparing bronchoalveolar lavage microbiological culture positivity between right versus left single lung transplants

Kevin Zhang (1), Gregory Berra (1), Mitsuaki Kawashima (1), Eyal Fuchs (1), Ella Huszti (2), Meghan Aversa (1), Rasheed Ghany (1), Shahid Husain (1), Jussi Tikkanen (1), Jonathan Yeung (1), Tereza Martinu (1)

cykevin.zhang@mail.utoronto.ca

1. Toronto Lung Transplant Program, University Health Network.
2. Biostatistics Research Unit, University Health Network.

Introduction & Objectives: Lung transplant recipients are at elevated risk of aspiration and subsequent microbial colonization and infection of the lungs, which portend worse clinical outcomes. Although aspiration is thought to affect the right lung more commonly than the left lung due to anatomical factors, such association has not been shown in lung transplant recipients. We hypothesized that bronchoalveolar lavage (BAL) from right single lung transplants (SLT) have higher microbiological culture positivity compared to BAL from left SLT, leading to worse outcomes in right SLT recipients.
Methods: All first adult SLT performed at our institution up to June 2021 with at least one BAL microbiological culture result were included. All BAL from surveillance and clinically indicated bronchoscopies were included. By our protocol, BAL is obtained from the transplanted lung, either the right middle lobe or lingula, unless clinically indicated otherwise. Fisher's exact test and univariable Cox proportional hazards model were used to compare culture positivity and outcomes, respectively.
Results: 165 right SLT recipients with 1505 cultures and 164 left SLT recipients with 1450 cultures were included. Baseline patient characteristics were comparable. BAL from right SLT had 17% positivity for significant respiratory pathogens, compared to 12% from left SLT ($p<0.0001$). Right SLT had higher positivity for P. aeruginosa (7% right vs. 4% left, $p<0.001$) and S. aureus (2% right vs. 1% left, $p<0.04$). There was similar positivity for high commensal flora (34% right vs. 36% left, $p=0.26$). There was a trend towards lower risk of chronic lung allograft dysfunction (HR 0.77 [0.55-1.09], $p=0.1$) and death/retransplant (HR 0.76 [0.58-1.01], $p=0.06$) in right SLT recipients.
Conclusion: BAL from right SLT have higher BAL microbiological culture positivity for significant respiratory pathogens, P. aeruginosa, and S. aureus compared to BAL from left SLT, with a trend toward better outcomes in right SLT recipients.

Abstract #31

Comparison of cardiac structure and function of patients with heart failure with reduced ejection fraction with and without sleep-disordered breathing

Shoichiro Yatsu (1, 2), Christian M. Horvath (1, 2), Tomoyuki Tobushi (2, 3), Anna Woo (2, 3), John S. Floras (2, 3), Alexander G. Logan (2), T. Douglas Bradley (1, 2) on behalf of the ADVENT-HF investigators.

Shoichiro.Yatsu@uhn.ca

1. Sleep Research Laboratories of the University Health Network, Toronto Rehabilitation Institute (KITE) and Toronto General Hospital and University of Toronto, Toronto, Canada
2. Department of Medicine, University Health Network, Sinai Health System and University of Toronto.
3. Peter Munk Cardiac Center, University Health Network, Toronto, Ontario, Canada

Introduction: In patients with heart failure with reduced ejection fraction (HFrEF), sleep-disordered breathing (SDB) may affect, or be affected by cardiac structure and function. Previous studies suggest that patients with central sleep apnea (CSA) have worse cardiac function and higher mortality than those without SDB, but no studies have been large enough to confirm this possibility. In addition, in HFrEF patients, cardiac structure and function correlates have not been examined in relation to the presence of CSA, OSA and no SDB (NSDB). We hypothesized that in patients with HFrEF, those with CSA would have a greater degree of left ventricular (LV) remodeling and impaired LV function than those with OSA or NSDB, and those with OSA would be intermediate between the other 2 groups.
Methods: ADVENT-HF is a multinational randomized trial investigating the effects on morbidity and mortality of treating SDB by adaptive servo- ventilation in patients with HFrEF. Inclusion required LV ejection fraction (LVEF) ≤45%, and an apnea-hypopnea index (AHI) ≥15 on a polysomnogram (PSG). Subjects with an AHI <15 were excluded from randomization but comprised a NSDB control group. All transthoracic echocardiograms (TTE) and PSGs were analyzed in core laboratories at University Health Network in Toronto. Patients with SDB were subdivided into those with OSA and those with CSA. We then compared baseline demographic and TTE characteristics of the NSDB, OSA and CSA cohorts.
Results: Among them, 678 with acceptable TTE were analyzed. As shown in the table, the CSA group was older, more predominantly male, and had a higher AHI than the other groups, and a higher prevalence of atrial fibrillation and a lower minimum arterial oxyhemoglobin saturation level than the NSDB group. The CSA group also had greater LV mass index than the other groups, greater LV volume indices and lower LVEF than the OSA group, and lower cardiac index than the NSDB group. Although the OSA group had no significant differences in TTE findings compared to the NSDB group, the OSA group was older, more predominantly male, and had a greater AHI than the NSDB group and a higher BMI than the CSA group and lower minSaO2 than the other groups.
Conclusion: In patients with HFrEF, the degree of LV remodeling and dysfunction did not differ between the OSA and NSDB groups, but those with CSA had more advanced LV remodeling and dysfunction than the other groups signaling more advanced HF. These findings suggest that, in

patients with HFrEF, CSA is sign of worse cardiac structure and function than in patients with OSA and NSDB, and this may contribute to their higher mortality rate.

	NSDB n=50	OSA n=448	CSA n=180	p
Age, yr	55.9±11.8	61.2±10.1*	65.4±11.3*†	<0.0001
Male, (%)	28(60.9)	367(83.6) *	171(95.5) *†	<0.0001
BMI, kg/m^2	28.4±5.47	31.1±6.97	28.8±13.7†	0.0084
AF, (%)	6(13)	109(24.9)	59(33.3) *	0.0096
AHI, /hour	8.52±3.84	39.3±20.2*	50.8±18.0*†	<0.0001
minSaO_2, %	86.4±5.37	78.6±11.8*	80.6±8.51*†	<0.0001
NYHA class III or IV, (%)	8 (17.4)	102 (23.2)	46 (25.2)	0.5117
LVMI, g/m^2	112.4±30.0	119.3±34.2	132.1±40.0*†	<0.0001
LVEDVI, mL/m^2	113.0±40.0	103.0±33.7	111.8±41.8†	0.0157
LVESVI, mL/m^2	79.9±36.2	72.4±29.9	82.4±38.9†	0.0132
LVEF, %	31.8±7.99	32.0±7.80	29.0±8.43†	0.0001
CI, L/min	2.29±0.70	2.07±0.65	1.95±0.54*	0.098
At least moderate MR, (%)	7(15.2)	32(7.3)	23(12.8)	0.0299

Values are mean ± SD, n (percent).
AF, atrial fibrillation; AHI, apnea hypopnea index; BMI, body mass index; CI, cardiac index; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end diastoric volume index; LVESVI, left ventricular end systolic volume index; LVMI, left ventricular mass index; MR, mitral regurgitation; minSaO2, minimum arterial oxyhemoglobin saturation; *p < 0.05 versus NSDB. †p < 0.05 versus OSA.

Abstract #32

Relationship between Airflow Limitation in Response to Upper Airway Negative Pressure During Wakefulness and Obstructive Sleep Apnea Severity

Jan Lim (1), Hisham Alshaer (2), Nasim Montazeri Ghahjaverestan (1, 3), T. Douglas Bradley (1, 4, 5).

jan.lim@mail.utoronto.ca

1. KITE Sleep Research Laboratory, Toronto Rehabilitation Institute of the University Health Network.
2. Pragmatic Innovation Inc.
3. Institute of Biomedical Engineering, University of Toronto.
4. Department of Medicine, Toronto General Hospital of the University Health Network.
5. Department of Medicine, University of Toronto.

Study Objectives: To determine whether alteration in airflow induced by negative pressure (NP) applied to participants' upper airways during wakefulness, is related to obstructive sleep apnea (OSA) severity as determined by the apnea-hypopnea index (AHI).
Methods: Male and female adult participants referred for polysomnography (PSG) because of a suspicion of a sleep disorder were recruited. All participants underwent overnight PSG to assess their AHI. Subsequently, while awake, participants were twice exposed to -3 cm H2O of NP, which was applied orally and automatically at the onset of expiration and terminated after five full breaths. The ratio of the airflow of the last two breaths during NP exposure to the last two breaths prior to NP exposure was deemed the NP airflow ratio (NPR).
Results: Eighteen participants were enrolled. There was an exponential relationship between AHI and NPR. Because this relationship was exponential, NPR was exponentially transformed and labelled ExpNPR. A strong relationship between the AHI and ExpNPR for all participants was observed ($R2 = 0.55$, $p < 0.001$). AHI and ExpNPR were also more strongly correlated in male participants ($R2 = 0.87$, $p < 0.001$) than the whole group. A multivariable model (see Table below) using ExpNPR, age, BMI and sex accounted for 81% of variability in AHI ($p = 0.0006$). Finally, a leave-one-subject-out cross-validation analysis revealed that the predicted AHI using the multivariable model, and the actual AHI from participants' PSGs, were strongly related ($R2 = 0.72$, $p < 0.001$).
Conclusions: We have developed a novel measure of UA collapsibility that is simple, rapid, and can be easily applied during wakefulness. NPR or ExpNPR, was strongly related to the AHI, independently of demographic factors known to be related to the AHI. Inclusion of demographic factors to the NPR in a multivariable model provided an even stronger predictor of OSA severity and could account for 81% of the variability in the AHI.

Table: Multivariable Regression Analysis Between the AHI and Independent Variables

Variable	**Estimate**	**SE**	***P***	**Partial R^2**
Age	0.52	0.21	0.032	0.062
BMI	0.66	0.57	0.27	0.092
Sex	10.02	7.81	0.22	0.15
Sex*ExpNPR	17734.23	6267.033	0.015	0.086
ExpNPR	-2679.72	5984.93	0.66	0.48
Total Model	$R^2 = 0.87$; adjusted $R^2 = 0.81$; $F_{5, 12} = 15.82$; p-value: 0.0006			

Multivariable regression analysis revealed that age, BMI, sex and ExpNPR accounted for over 80% of variability in AHI scores in all participants. ExpNPR was the single most important contributor to the overall model, with a partial R^2 value of 0.48.