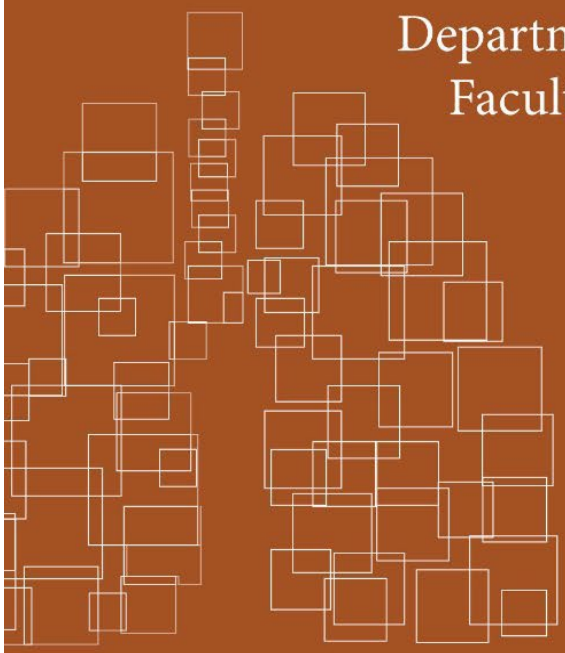
Annual Research & Award Day
Division of Respirology 2023

Friday June 9, 2023
9:00-16:00

The Faculty Club - University of Toronto
41, Willcocks street

www.respirologyresearch.com

Division of Respirology
Department of Medicine
Faculty of Medicine



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UNIVERSITY OF TORONTO

PROGRAM – Annual Research & Award Day 2023 – June 9, 2023

Location: The Faculty Club – University of Toronto – 41, Willcocks Street

8:15 Registration and Poster Set-up

8:15 – 9:15 Coffee & Breakfast. 

9:15 – 9:30 Opening of the Respirology Research Day: **D. Rozenberg & G Montandon.** Director of the Division of Respirology – **Dr. Chung-Wai Chow**.

9:30 KEY-NOTE SPEAKER:

Dr. Gregory P Downey, M.D. FRCPC

Professor of Medicine, Pediatrics and Immunology and Genomic Medicine National Jewish Health - University of Colorado School of Medicine
President, American Thoracic Society

Research Highlights from the Respirology Division over the Decades

10:00 – 10:30 Coffee/Stretch Break 

10:30 – 11:30 SESSION 1 - Basic & Translational Science

10:30 **Raina Ladha**. Optical interrogation of cholinergic and glutamatergic pre-motor inputs to a medullary circuit essential to rhythmic breathing (Abstract #27)

10:42 **Kayla S. Baker.** Role of inhibitory brainstem cells in controlling respiratory rhythms (Abstract #33)

10:54 **Allen Duong.** Isolation and characterization of osteopontin-expressing pulmonary macrophages associated with chronic lung allograft dysfunction in humans (Abstract # 3)

11:06 **Wenshan Zhong.** Club Cell Secretory Protein (CCSP) Treatment in a Mouse Model of Chronic Lung Allograft Dysfunction (CLAD) (Abstract # 4)

11:18 **K. F. Bei.** Regulatory T Cells in Chronically Rejected Human Lung Allografts Exhibit A Gene Expression Program Suggesting Dysfunction (Abstract # 25)

11:30 KEY-NOTE SPEAKER:

Dr. Nick Hanania, M.D. MS

Director, Airways Clinical Research Center
Professor of Medicine, Baylor College of Medicine

Confronting COPD in the Era of Personalized Medicine

12:00 - 13.30 Lunch break 

12:15 - 13:30 Poster Viewing & Judging

13:30 - 14:30 SESSION 2 – Clinical and Health Sciences

13.30 **Shoichiro Yatsu.** Effect of peak airflow-triggered adaptive servo-ventilation on the sleep apnea and sleep structure in patients with heart failure and sleep disordered breathing (Abstract # 7)

13:42 **Amanda Mac.** Machine Learning Using MiniRocket Improves the Diagnostic Acumen of Spirometry (Abstract # 15)

13.54 **Noor Al Kaabi.** Respiratory Symptoms, Health-Related Quality of Life, and Symptom Management in Ehlers-Danlos Syndrome and Generalized-Hypermobility Spectrum Disorders (Abstract # 9)

14:06 **Abarnaa Illango.** Changing demographics of individuals with Cystic Fibrosis transitioning from pediatric to adult care (Abstract # 29)

14:18 **Jordan Sugarman.** Trends in Prevalence of Chronic Obstructive Pulmonary Disease in Immigrants to Ontario, Canada, 2002-2019 (Abstract # 22)

14:30 KEY-NOTE SPEAKER:

Dr. Smita Pakhale, M.D.MSc, FRCPC

Clinical Research Chair in *Equity & Patient Engagement in Vulnerable Populations*
Scientist - Ottawa Hospital Research Institute
Associate Professor - University of Ottawa, The School of Epidemiology and Public Health
Staff Respirologist- Division of Respiratory Medicine, Ottawa Hospital

The Bridge Model™ - Why should we Build Bridges to fill the gap in Healthcare delivery (with a comprehensive approach)

15:00 - 15:30 SNACKS/REFRESHEMENTS & Judges Decide on Oral/Poster Winners

Fruits and sweets, cheese and charcuterie platter, refreshments, cash bar

15.30 -16:00 Awards and Prizes of the Division of Respirology

Awards ceremony for Research: G. Montandon

Faculty Research and Trainee Awards: D. Rozenberg

Other Division Respirology Awards

Organizers:

Dr. Dmitry Rozenberg
Dr. Gaspard Montandon
Ms. Rhiannon Davies

Abstract Judges:

Dr. Marie Faughnan
Dr. Gaspard Montandon
Dr. Clodagh Ryan
Dr. Dmitry Rozenberg
Dr. Nick Vozoris

Awards of Division of Respirology

Jae Yang Award 2022-23 recipient:

Dr. Waleed Ahmed

Sheldon Mintz Faculty Teaching Award 2022-23

Dr. Harvey Wong

Faculty Excellence in Research Award 2022-2023:

Dr. Anne Stephenson

Outstanding Research Trainee Award 2022-2023:

Dr. Anastasiia Vasileva

Keynote Speaker:

Gregory P. Downey MD FRCP(C) ATSF

Executive Vice President for Academic Affairs
Professor, Departments of Medicine, Pediatrics and Immunology and Genomic Medicine
National Jewish Health

Associate Dean and Professor,
Departments of Medicine
Immunology and Microbiology
University of Colorado School of Medicine
President, American Thoracic Society (2022-2023)

Dr. Downey received his MD from the University of Manitoba and completed Internship and Residency in Internal Medicine at Harvard Medical School, Beth Israel and Brigham and Women's Hospital, Boston. He then completed clinical training in Pulmonary and Critical Care Medicine at the University of Colorado, Denver. He undertook post-doctoral research training in Immunology in the laboratory of Dr. Peter Henson at National Jewish Health. He was appointed Assistant Professor at the University of Toronto rising through the ranks to become the Director of the Division of Respirology, Professor and Vice-Chair, Department of Medicine, and the recipient of a Tier 1 Canada Research Chair in Respiration Sciences.

Dr. Downey returned to Colorado as Executive Vice President of Academic Affairs and Provost and Professor of Medicine, Pediatrics, and Immunology and Genomic Medicine at National Jewish Health, and Professor of Medicine and Immunology and Microbiology and Associate Dean of the School of Medicine, University of Colorado. His current research interests include innate immunity, signaling mechanisms involved in acute lung injury/ARDS, the effects of particulate matter exposure on lung health, and mechanisms and treatment of pulmonary fibrosis. His research has been funded by the National Institutes of Health, the Canadian Institutes of Health Research, and the US Department of Defense for over 30 years.

Dr. Downey has >250 publications in top ranked journals including the *New England Journal of Medicine*, *Science*, *Science Translational Medicine*, *Nature Cell Biology*, the *Journal of Cell Biology*, the *American Journal of Respiratory and Critical Care Medicine*, the *Journal of Experimental Medicine*, *Blood*, *PNAS*, the *American Journal of Respiratory Cell and Molecular Biology,* and the *Journal of Immunology* and his work has been cited over 23,000 times by other authors (*h*-index 83). Dr. Downey is a member of the American Society for Clinical Investigation, the Association of American Physicians, the American Thoracic Society, the American College of Chest Physicians, the Royal College of Physicians and Surgeons of Canada. He currently serves as the Immediate Past President of the American Thoracic Society.

Keynote Speaker

Nicola A. Hanania, MD, MS, FCCP, FACP, FRCP(C), FERS

Professor of Medicine, **Section of Pulmonary and Critical Care Medicine**
Director, **Airways Clinical Research Center**
Baylor College of Medicine

Chief**, Section of Pulmonary and Critical Care Medicine, Ben Taub Hospital**
Clinical Science Representative**,**
BCM Faculty Senate

Nicola (Nick) A. Hanania, MD, MS, is professor of medicine in the Section of Pulmonary and Critical Care Medicine and director of the Airways Clinical Research Center at the Baylor College of Medicine in Houston, Texas. He is Chief of Section of Pulmonary, Critical Care and Sleep Medicine at Ben Taub Hospital. He completed his medical training at the University of Jordan in Amman, Jordan, followed by a residency in internal medicine and a fellowship in pulmonary medicine at the University of Toronto, Toronto, Canada. He subsequently completed a fellowship in critical care medicine at Baylor College of Medicine, where he later earned a master's degree in clinical investigation.

Dr Hanania has received multiple awards, including the ACCP's Distinguished Scholar in Respiratory Health, Baylor College of Medicine's Master Clinician Award, Distinguished CHEST educator (DCE) 2017-2022, ACCP Humanitarian Award, Career Investigator Award (K23) from the National Institutes of Health, Fulbright and Jaworski's Faculty Excellence Award for Teaching and Evaluation, the Award for Excellence in Teaching from the Department of Medicine and attending of the year of the Section of PCCM at Baylor College of Medicine. He is editor-in-chief of *Respiratory Medicine* and is associate editor of the journals, *Current Opinion in Pulmonary Medicine* (Asthma Section), and *Lung*. He serves on the editorial board of *Therapeutic Advances in Respiratory Disease, Pulmonary Pharmacology and Therapeutics, COPD (J of COPD Foundation)*.

Dr Hanania's research interests focus on the pharmacology and management of asthma and COPD. His research has been funded by NIH, ALA and industry and focuses on clinical trials investigating novel treatments. He has published more than 320 peer-reviewed papers, book chapters, editorials, and reviews on these topics. He has been invited and has lectured widely at local, regional, national, and international meetings.

Keynote Speaker

Dr. Smita Pakhale, MD, MSc, FRCPC

Clinical Research Chair in *Equity & Patient Engagement in Vulnerable Populations*
Scientist - Ottawa Hospital Research Institute

Associate Professor - University of Ottawa
The School of Epidemiology and Public Health
Staff Respirologist- Division of Respiratory Medicine,
Ottawa Hospital

Dr. Smita Pakhale, a clinician-scientist at the Ottawa Hospital and Ottawa Hospital Research Institute (adult pulmonologist) and a Associate Professor at the School of Epidemiology and Public Health, Univ. of Ottawa, Canada since 2008. She holds the Clinical Research Chair in *Equity & Patient Engagement in Vulnerable Populations.* She is leading community-based research projects at the Bridge Engagement Centre (the Bridge), at 225 Donald St in Ottawa. The Bridge conducts research projects in true partnership with people who have lived and living experience of poverty, homelessness, at-risk for homelessness, and low-income racialized populations, including Indigenous peoples. The Bridge has designed and operationalized a 'Patient Engagement' model, the Bridge Model™, which has been acclaimed internationally.

Dr. Pakhale completed her post-graduation training in Internal Medicine at the Columbia Univ., NYC, and later did fellowships at the University of Toronto and Univiversity of Manitoba. Most recently, she completed a Master's degree in Epidemiology and Biostatistics at the McGill University.

Authors' List

Abstract	First	Last	Email	Oral or Poster #
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2	Allen	Duong	allen.duong@mail.utoronto.ca	P2
3	Allen	Duong	allen.duong@mail.utoronto.ca	Oral
4	Wenshan	Zhong	wenshan.zhong@uhnresearch.ca	Oral
5	Waleed	Ahmed	ws.ahmed@mail.utoronto.ca	Not available
6	Waleed	Ahmed	ws.ahmed@mail.utoronto.ca	P3
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P = poster presentation; O = oral presentation

Posters: 1 to 10 (Transplantation; Advanced Lung Disease/Physical Function)
Posters: 11 to 14 (Sleep); **Posters: 15-17** (Cystic Fibrosis)
Posters: 18-21: Oscillometry/Lung Function; **Posters: 22-25:** Malignancy/Rehab/NTM

Abstracts:

Abstract 1:

A rapid collagenase A-based dissociation strategy of human lung tissue maximizes cell yield and minimizes cellular stress responses

Allen Duong (1), Aaron Wong (1), Rayoun Ramendra (1), Shaf Keshavjee (1), Mingyao Liu (1), Stephen Juvet (1), Tereza Martinu (1)

1. Toronto Lung Transplant Program, University Health Network, University of Toronto.

Introduction & Objectives: The human lung is a highly heterogeneous organ, that is more complex when taking disease states into consideration. To obtain single cells for experimental assays, lung tissue dissociation involves mechanical and enzymatic disruption. However, variables such as time, temperature, and enzymes used can lead to cell injury or death, reducing experimental yield and utility. We developed a novel protocol, ColShort, that reduces the dissociation time with the intent of maximizing cell yield and diversity. We compared ColShort with four established protocols in the literature to determine its utility.

Methods: Three idiopathic pulmonary fibrosis lung tissue samples were obtained during lung transplantation and divided into 5 groups of equal mass: collagenase A short (ColShort), collagenase A long (ColLong), liberase elastase (LibElas), collagenase A dispase (ColDis) and collagenase A cold-protease (ColCold). Lung tissues were processed into single cell suspensions according to each protocol. Cell yield and viability was measured using a hemocytometer. Multiparameter flow cytometry was performed to assess for cell types. qRT-PCR was used to assess expression of stress response genes FOS, DUSP1, and NR4A1.

Results: Compared to all other protocols, ColShort provided the highest cell yield with no change in cell viability. LibElas, ColDis and ColCold had significant reductions in several cell populations including CD4 and CD8 T cells, and macrophages. Among stress response genes, ColShort had the lowest expression of FOS, DUSP and NR4A1.

Conclusion: The ColShort protocol, used on fibrotic lung tissue, provides the highest cell yield with no reduction in viability or observed loss in cell surface markers. This implies that a short dissociation time is advantageous when processing fibrotic human lung tissue for single-cell analyses. Future studies are required to assess the application of ColShort in non-fibrotic tissue.

Abstract 2:

Semi-supervised machine learning algorithm reveals human lung EVLP perfusate cell populations are associated with donor mode of death and post-transplant primary graft dysfunction

Allen Duong (1), Goodness Madu (1), Sajad Moshkelgosha (1), Jonathan Yeung (1), Marcelo Cypel (1), Shaf Keshavjee (1), Tereza Martinu (1), Stephen C Juvet (1)

1.Toronto Lung Transplant Program, University Health Network, University of Toronto.

Introduction and purpose: Lung transplantation (LT) is limited by the lack of suitable donor lungs, and early-post LT survival is hampered by primary graft dysfunction (PGD). Both neurological determination of death (NDD) and donation after circulatory death (DCD) are associated with donor lung injuries, and ex vivo lung perfusion (EVLP) can be used to assess donor lung suitability. The relationship of leukocytes within the EVLP perfusate to donor mode of death and PGD is not well studied. Using CITRUS, an algorithm identifying stratifying biological signatures, we hypothesized that there would be differences in perfusate leukocyte composition based on donor mode of death and recipient PGD status.

Methods: Clinical EVLP cases from donor lungs of NDD (n=20) and DCD (n=20) origin were retrospectively selected. In a separate cohort, clinical EVLP cases were selected and grouped based on recipient PaO2/FiO2 ratio at 72h post-LT into two groups: PGD3 (n=33) and PGD0/1 (n=25). Cryopreserved perfusate cells were subjected to flow cytometry and then underwent CITRUS analysis, comparing NDD to DCD and PGD0/1 to PGD3 to identify significantly stratifying cell populations ($p < 0.01$).

Results: When comparing perfusate cells between NDD and DCD, NK cells and macrophages were observed to be higher in NDD whereas memory T cells were enriched in DCD. In the comparison of PGD0/1 and PGD3, neutrophils (Nφ) were found to be significantly higher in the PGD3 whereas NK cells were significantly higher in the PGD0/1 group.

Conclusion: We have shown that certain perfusate cell populations are enriched based on donor mode of death, possibly due to distinct donor lung injury. The association of Nφ with PGD3 suggests a potential biomarker and therapeutic target. This work illustrates the value of cellular analysis of acellular EVLP perfusate, as all cells in the perfusate emanate from the donor lung and reflect its status.

Abstract 3:

Isolation and characterization of osteopontin-expressing pulmonary macrophages associated with chronic lung allograft dysfunction in humans

Allen Duong (1), Sajad Moshkelgosha (1), Rayoun Ramendra (1), Mingyao Liu (1), Boris Hinz (2), Shaf Keshavjee (1), Stephen Juvet (1), Tereza Martinu (1)

1. Toronto Lung Transplant Program, University Health Network, University of Toronto. 2. Faculty of Dentistry, University of Toronto

Introduction & Objectives: Chronic lung allograft dysfunction (CLAD) continues to be the primary cause of mortality in lung transplant recipients. Macrophages (MΦ) are an abundant population of immune cells in the lung and serve homeostatic and immunoregulatory functions, but their contribution to CLAD is not clear. Our single cell RNA sequencing (scRNAseq) data suggested that distinct MΦ subsets expressing osteopontin (SPP1) and other pro-fibrotic genes is present in CLAD lungs. We hypothesized that SPP1 MΦ have important pro-fibrotic properties in CLAD. Here, we isolated SPP1 MΦ by fluorescence-activated cell sorting (FACS) to assess their in vitro function.

Methods: scRNAseq data from 9 CLAD lungs obtained at re-transplantation or autopsy were analysed for surface proteins-coding genes in SPP1 MΦ, allowing us to develop antibody panels to FACS sort SPP1 MΦ and verify protein expression of SPP1. qRT-PCR was performed to confirm expression of fibrosis-associated MPP9 gene. Sorted SPP1 MΦ were put into culture.

Results: Analysis of cell surface protein-coding genes through scRNAseq revealed that SPP1 MΦ express SDC2 transcript, which show minimal expression in non-SPP1 MΦ clusters. Flow cytometry showed co-expression of surface SDC2 protein with intracellular SPP1 protein in CLAD lung MΦ and FACS was used to isolate SDC2+ and SDC2- MΦ. qRT-PCR showed that SDC2+ MΦ expressed more MMP9 transcripts than SDC2- MΦ. Sorted SDC2+ and SDC2- MΦ were then cultured.

Conclusion: We have shown that we are able to: 1) sort the SPP1 MΦ from human CLAD lungs based on SDC2 expression, 2) that sorted SDC2+ MΦ express SPP1 protein and MMP9 transcripts, and that sorted SDC2+ MΦ can be maintained in culture. In future work, the effect of SDC2 MΦ culture supernatant on lung fibroblast function will be assessed in wound-healing and collagen gel contraction assays as measures of fibroblast migration and contractility, characteristics of fibrosis."

Supported by: Sanofi

Abstract 4:

Club Cell Secretory Protein (CCSP) Treatment in a Mouse Model of Chronic Lung Allograft Dysfunction (CLAD)

Wenshan Zhong (1), Jillian Oliver (1), Olivia Mekhael (1), Zoeen Carter (1), Shaf Keshavjee (1), Aprile L. Pilon (2), Andrew E. Gelman (3), Stephen C Juvet (1), Tereza Martinu (1)

1. Toronto Lung Transplant Program, University Health Network, Toronto, ON, Canada

2. APCBio Innovations, Inc. & Trove Therapeutics, Inc., Rockville, MD 3Washington University School of Medicine, St. Louis, Missouri, USA

Introduction & Objectives: CLAD is the main limitation to long-term survival after lung transplantation. Airway epithelial injury, with loss of epithelial club cells and club cell secretory protein (CCSP), is thought to be a major step in CLAD pathogenesis. Recombinant human (rh)CCSP has been shown to have anti-inflammatory, anti-fibrotic, and pro-epithelial properties in animals; and anti-inflammatory effects in a human neonatal trial. However, effects of rhCCSP in CLAD remain unknown. We hypothesized that rhCCSP would prevent CLAD via decreasing epithelial injury, inflammation and fibrosis in a mouse model.

Methods: We used our established model of CLAD-like airway fibrosis, using C57BL/6 mice that received a minor alloantigen-mismatched orthotopic lung transplant from C57BL/10 donors, followed by 8 intratracheal (IT) lipopolysaccharide (LPS) doses administered on postoperative days (POD) 3-21. Intravenous (IV) or IT rhCCSP was administered on the day following each LPS, with an additional 5 doses on POD22-26. Lung samples were collected on POD28. CLAD-like pathological features were graded using H&E and Masson-Trichrome-stained histology samples. Flow cytometry was used to characterize immune cells and epithelial cells.

Results: In route/dose finding experiments, IV administrations of 2.4mg/kg rhCCSP resulted in greatest effects on fibrosis (data not shown). IV 2.4mg/kg rhCCSP significantly decreased vascular fibrosis with a trend towards reduced bronchiolitis obliterans scores, percent parenchymal fibrosis, peri-airway fibrosis, and epithelial hyperplasia, a marker epithelial injury (Fig 1A-F). There was no change in inflammation scores (Fig 1G). In addition, a significantly higher frequency of proliferating Ki67+ club cells, and a trend towards higher frequency of epithelial cells and club cells, were observed in the rhCCSP group by flow cytometry (Fig 1H-J). In contrast, we found no differences in immune cells (Fig 1K-L).

Conclusions: rhCCSP treatment may attenuate fibrosis and potentiate epithelial repair through immune-independent pathways in an LPS-induced mouse model of CLAD. Further experiments are needed to investigate how CCSP regulates epithelial changes and fibrosis.

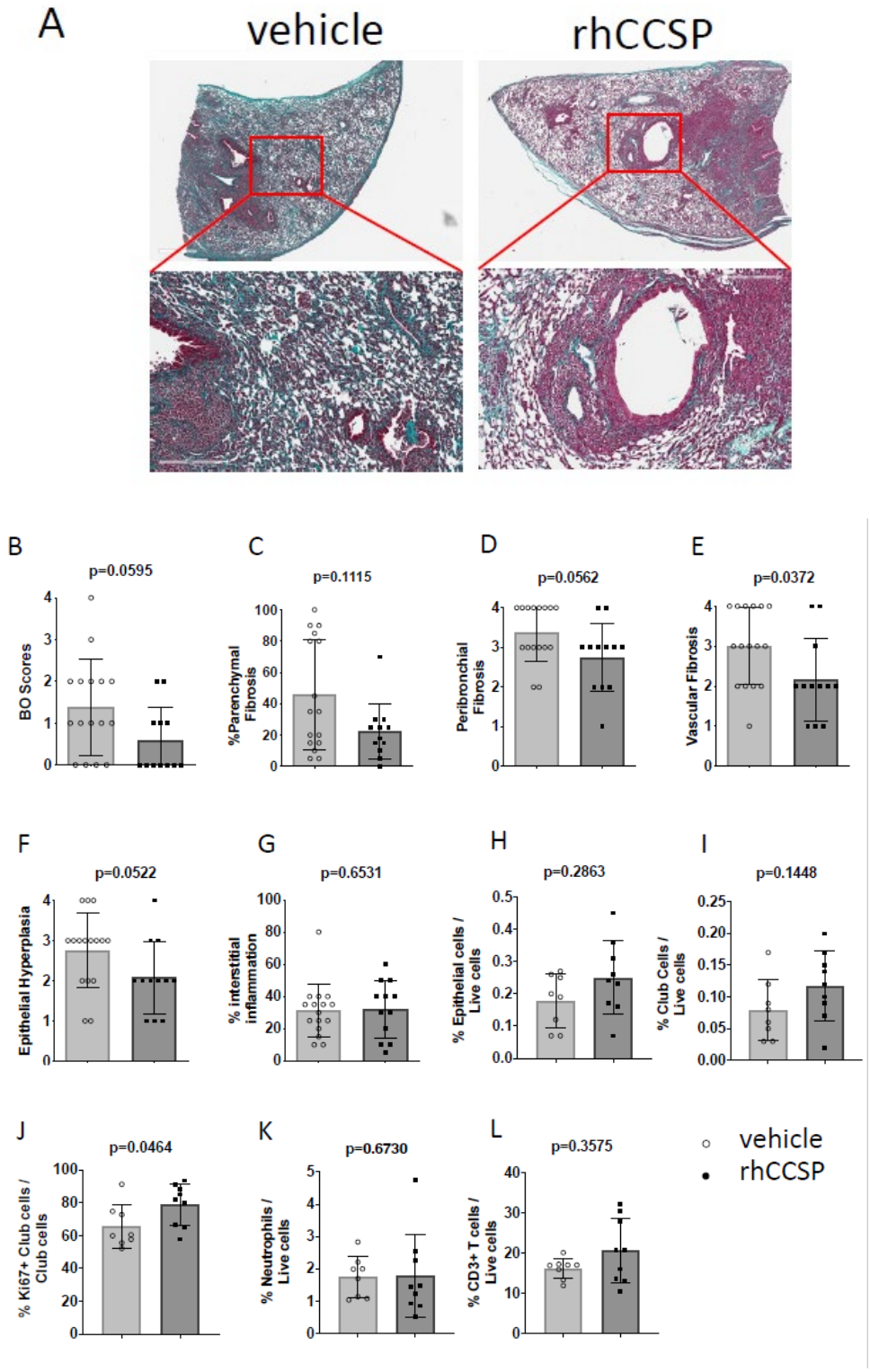

Figure 1: rhCCSP was administrated to C57BL/6 recipients of C57BL/10 allografts in the context of LPS stimulation (n=16 or n=8 per group) . POD28 endpoints are shown. Mann-Whitney test was used.

Abstract 5:

Influence of depression and anxiety on health-related quality of life while awaiting lung transplant

Waleed Ahmed (1), Noori Chowdhury (2), Sunita Mathur (3), Susan Abbey (4), Lianne Singer (5)

1. Division of Respirology, Department of Medicine, University of Toronto, 2. Toronto Lung Transplant Program, University Health Network (UHN), 3. Department of Physical Therapy, UHN, 4. Department of Psychiatry, UHN, 5. Division of Respirology, Department of Medicine, UHN, Toronto, ON, Canada

Introduction: Severe lung disease has significant effects on mental health, which is exacerbated by the stress of awaiting lung transplantation (LTx). The prevalence of depression and anxiety in LTx candidates and their effects on health-related quality of life (HRQL) has not been well described.

Methods: The Frailty and Sarcopenia in Organ Transplantation study (FROST) is a prospective single-center cohort study of 240 adults listed for solid organ transplantation. Of 70 subjects on the LTx list, we evaluated the 65 with complete data. Prior to transplant, these patients completed the PHQ-9 to screen for depression, GAD-7 to screen for anxiety, and the SF-12 to evaluate HRQL with both physical and mental components. Using multiple linear regression adjusted for age, gender, and diagnosis, we identified whether depression or anxiety was associated with the SF12 MCS or PCS.

Results: 50% of participants were female, with an average age of 59 (SD 13.3). The most common diagnoses were interstitial lung disease (46%), and chronic obstructive pulmonary disease (38%). The average PHQ9 score was 7.2 (mild depression). 69% of patients had depression of whom 22% had moderate to severe depression. Average GAD7 score was 4.2 corresponding to no anxiety and 6.2% of patients had moderate to severe anxiety. Patients with depression had a lower mean SF12 MCS than those without (46 vs. 55, $p = 0.001$), but there was no significant difference between PCS scores. Patients with anxiety had a lower MCS (43 vs. 53, $p = 0.005$), and PCS (30 vs. 34, $p = 0.03$) than those without anxiety.

Conclusion: More LTx candidates in this cohort had depression than anxiety; both were associated with significant reductions in mental HRQL. Anxiety was also associated with a reduction in physical HRQL. Screening and treatment for depression and anxiety may represent an opportunity to improve HRQL in lung transplant candidates.

Abstract 6:

Influence of pre-transplant cognitive impairment on post-transplant length of stay and delirium

Waleed Ahmed (1), Noori Chowdhury (2), Sunita Mathur (3), Susan Abbey (4), Lianne Singer (1, 5)

1. Division of Respirology, Department of Medicine, University of Toronto 2. Toronto Lung Transplant Program, University Health Network (UHN), 3. Department of Physical Therapy, UHN, 4. Department of Psychiatry, UHN, 5. Division of Respirology, Department of Medicine, UHN, Toronto, ON, Canada

Introduction: Organ transplantation is increasingly being offered to more medically complex patients. Advancing age may increase the risk of cognitive impairment in lung transplant (LTx) candidates, and increase the risk of adverse early post-transplant outcomes. We characterized the prevalence of cognitive impairment in LTx candidates and whether mild cognitive impairment (MCI) influenced hospital length of stay (LOS) or delirium.

Methods: Frailty and Sarcopenia in Organ Transplantation (FROST) is a prospective single-center cohort study of 240 adults listed for organ transplantation. Of 70 patients on the lung transplant list, we evaluated the 54 patients with complete data. We characterized the prevalence of MCI pre-transplant using the Montreal Cognitive Assessment. Chart review established LOS and development of clinically evident delirium requiring pharmacotherapy or a psychiatry consult. We did a Mann-Whitney U test to compare LOS in patients with or without cognitive impairment. Chi-squared test was used to evaluate whether MCI was related to the presence of delirium during hospitalization.

Results: The average age of candidates was 59.6 (standard deviation 13), 43% female. The most common diagnoses were interstitial lung disease (45%), and chronic obstructive pulmonary disease (41%). Average MoCA score was 26.4 (SD 2.46) and 18/53 (34%) candidates had a MoCA < 26 corresponding to MCI. Median length of stay was 22 days (7-100 days, IQR 19.5 days), 22 days in subjects without MCI, and 25.5 days in those with MCI. 22/53 patients (42%) had delirium, of whom 20 required antipsychotics as inpatients. Delirium incidence was 50% in patients with MCI and 37% in those without MCI. There was no association between MCI and post-transplant LOS, nor was there an association between MCI and delirium.

Conclusion: A significant proportion of transplanted patients in this sample had mild cognitive impairment. This was not associated with increased length of stay post-transplant, nor an increased risk of delirium."

Abstract 7:

Effect of peak airflow-triggered adaptive servo-ventilation on the sleep apnea and sleep structure in patients with heart failure and sleep disordered breathing

Shoichiro Yatsu (1), Christian M. Horvath (1,2), John S. Floras(2,3), Alexander G. Logan(2), Clodagh M. Ryan(1,2), T. Douglas Bradley(1,2)

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

Introduction: In patients with heart failure and reduced ejection fraction (HFrEF), sleep disordered breathing (SDB) disrupts sleep structure. However, there is little evidence that treating OSA or CSA in patients with HFrEF improves sleep structure. The Adaptive Servo-Ventilation for Therapy of Sleep Apnea in Heart Failure (ADVENT-HF) is multinational randomized trial investigating the effect of peak flow triggered ASV (ASVPF) in patients with HFrEF and SDB and found that ASVPF improved patients quality of life and daytime sleepiness. We hypothesized that such improvements may be associated with improved sleep structure.

Methods: This is an ancillary study of the ADVENT-HF trial. Following baseline polysomnography (PSG), patients with HFrEF (left ventricular ejection fraction ≤45%) and an apnea-hypopnea index (AHI) ≥15 events/h were randomized to control or ASVPF. One month later, both groups underwent a repeat PSG. We then compared changes in sleep structure from baseline to 1 month between the ASVPF and control groups.

Results: Among 731 patients, 335 randomized to control and 318 to ASVPF completed a 1 month PSG and were included in the analysis. As shown in the figure, compared to the control group, ASVPF significantly reduced the AHI in association with significantly greater increases in mean and minimum arterial oxyhemoglobin saturation (SaO2). It also reduced arousal frequency and caused a shift for the lighter stage to the deeper more restorative stages of sleep characterized by significantly greater decrease in stage N1, and significantly greater increases in stage N3 and REM sleep than in the control group.

Conclusion: These data are the first to demonstrate, in a large cohort of patients with HFrEF, that alleviation of OSA and CSA by ASVPF consolidates sleep through reductions in arousal frequency accompanied by a highly significant shift from lighter stages to deeper stages of sleep.

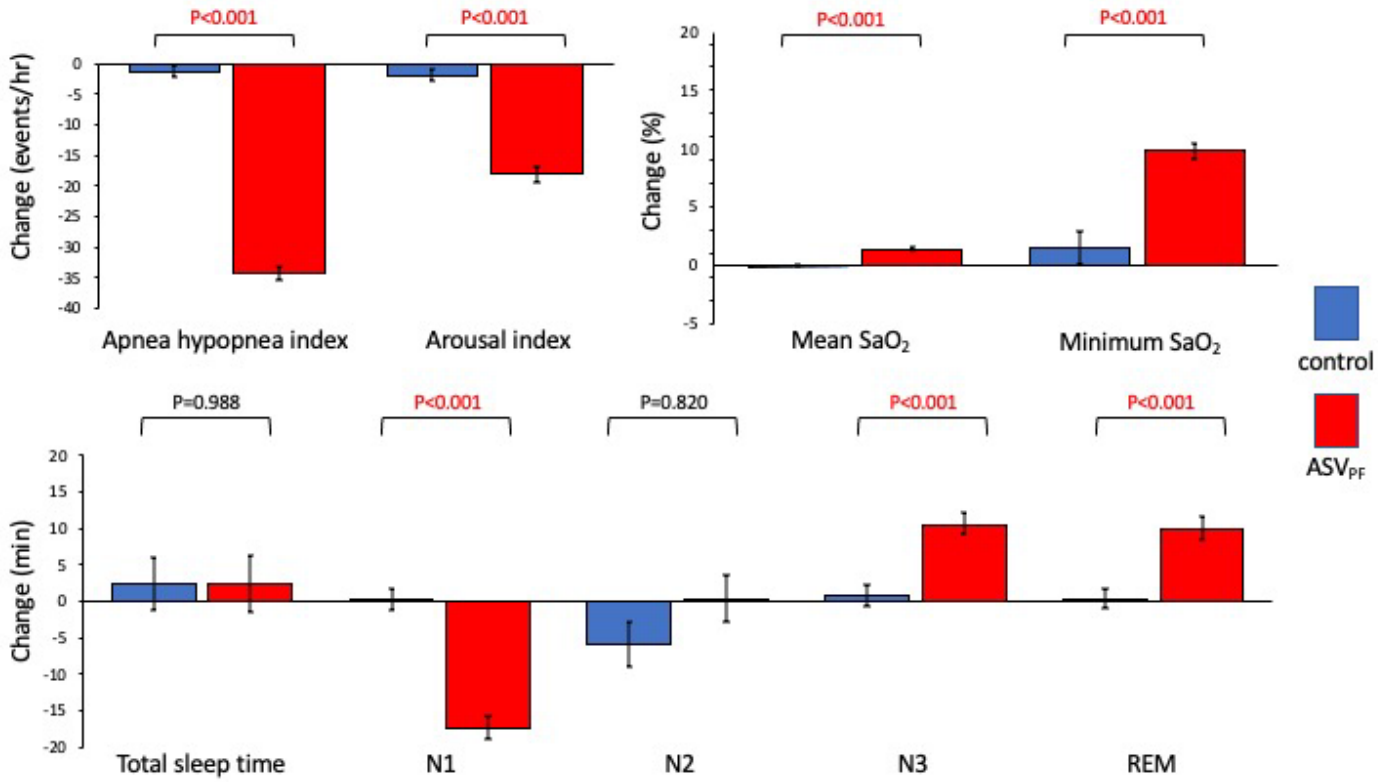

Figure: Illustration demonstrating Apnea hypopnea index of ASVPF compared to the control group.

Abstract 8:

Longitudinal Changes in Bone Mineral Density in Adult Cystic Fibrosis Patients

Reem Jad; Xiayi Ma; Sanja Stanojevic; Abarnaa Illango; Julie Gilmour; Christopher Goss; Lisa Strug; Anne L. Stephenson

St. Michael's Hospital

Introduction and Objectives: Cystic Fibrosis (CF) related bone disease is a common and multifactorial complication in the adult CF population. Our understanding of the longitudinal trends of bone loss in this population is limited. Our objective is to estimate the average rate of change in bone mineral density (BMD) in adults with CF over time.

Methodology: This is a retrospective longitudinal cohort study of individuals aged 25-48 years, followed at the adult CF clinic at St. Michael's Hospital between January 2000 and December 2021. Individuals with at least one dual-emission X-ray absorptiometry (DXA) scan were included. The primary outcome was the rate of change in BMD in g/cm2 at the lumbar spine (LS) and femoral neck (FN). BMD measurements after transplant or initiation of bisphosphonate or modulator therapy were excluded. We used a linear mixed effects model with a random intercept and random slope to estimate the average rate of decline in BMD.

Results: We analyzed a total of 1502 DXA scans in 500 patients. A total of 68% of subjects had two or more DXA scans in the study period. The annual rate of decline of FN BMD was -0.008 g/cm2/year (95% CI -0.009, -0.007), which did not significantly change after adjusting for factors associated with BMD. Similarly, LS BMD had an annual decline of -0.006 g/cm2/year (95% CI -0.007, -0.004) which was unchanged in the multivariable model. Pancreatic insufficient (PI) subjects had a significantly faster rate of decline at the FN (-0.010 for PI vs. -0.005 for pancreatic sufficient (PS)) and at the LS (-0.006 for PI vs. -0.002 for PS).

Conclusion: We found that bone loss in adults with CF was comparable in magnitude to the decline reported in peri-menopausal women1. Further research is needed to identify those at highest risk for rapid bone loss and prevent fractures.

Abstract 9:

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

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Background: Hypermobile Ehlers-Danlos Syndrome (hEDS) and Generalized Hypermobility Spectrum Disorders (G-HSD) are connective tissue disorders with multi-systemic manifestations. Respiratory symptoms in hEDS/G-HSD may be associated with a negative impact on health-related quality of life (HRQL), however, this has not been investigated. Furthermore, this population reports several unmet symptom management and care needs.

Objectives: (1) To characterize respiratory symptoms and their association with HRQL, functional capacity and fatigue and (2) identify the respiratory symptom experiences and management needs in hEDS/G-HSD.

Methods: A mixed methods study including adult hEDS/G-HSD patients experiencing respiratory symptoms or having underlying respiratory manifestations. Multivariable linear regression was used to evaluate the association between respiratory symptoms and HRQL (Short-Form 36), functional capacity (Duke Activity Index Score) and fatigue (Fatigue Severity Scale) captured via Patient Reported Outcome Measures (PROMs). Physical activity levels were assessed using Fitbits worn for 7 days. The qualitative description framework was applied to explore participants' experiences through individual interviews.

Results: 37 hEDS/G-HSD patients completed the PROMs (35 ± 12 years; 89% female). Dyspnea was associated with a lower physical component score on Short-From 36 (β= -20.1 95% CI [-27.5 to -12.7], p=0.001), lower Duke Activity Index score (β = -18.7 [-29.3 to -8.07], p=0.001), and higher fatigue severity scores (β= 15.7 [8.26 to 23.2], p=0.0002), independent of age, sex and EDS subtype in separate models. The mean daily step count (n=16) was 4203 ± 2589 (sedentary). Four themes were identified. Theme 1: Respiratory symptoms were perceived as 'invisible' and underrecognized in clinical care. Theme 2: Dyspnea contributed to the cycle of inactivity. Theme 3: A dyspnea-fatigue symptom cluster was identified. Theme 4: Coherent care plans were emphasized by patients to improve their respiratory care.

Conclusion: This is the first study to identify that dyspnea has a negative impact on the physical aspects of HRQL in EDS. The findings of this study may be used to guide clinical management such as addressing inactivity and respiratory symptoms in hEDS/G-HSD patients."

Supported: Canadian Institute of Health Research Canada Graduate Scholarship Master's Award, the Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine, and the GoodHope Ehlers-Danlos Syndrome Foundation Grant

Abstract 10:

Clinical Implications of Frailty Assessed during Hospitalization for Acute-Exacerbations of Interstitial Lung Disease

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Introduction & Objectives: Acute exacerbations of interstitial lung disease (AE-ILD) are associated with increased morbidity and mortality. It is important to identify risk factors associated with AE-ILD to assist prognostication and evaluation of functional trajectories post AE-ILD. Frailty, a biological syndrome characterized by decreased physiological reserve, has been shown to be prevalent in ILD in >50% of patients but has not been evaluated during the inpatient setting. Thus, we aimed to evaluate frailty and its association with clinical characteristics, physical function, and hospital course with AE-ILD.

Methods: Retrospective, single-center cohort study of consecutive AE-ILD patients (01/2015-10/2019) admitted to the respiratory medicine ward. Frailty was defined as a deficit score ≥0.25 based on an adapted 30-item cumulative frailty index, incorporating deficits such as comorbidities, functional limitations, and laboratory parameters. Demographics, comorbidities (Charlson comorbidity index: CCI), pre-exacerbation lung function and 6-minute walk distance (6MWD), and hospital outcomes were abstracted from chart review. Differences between frail and non-frail patients were compared using Mann-Whitney-U tests and chi-square tests.

Results: 89 people were admitted to hospital with an AE-ILD (age:67 years IQR:[62–71], 63%IPF, FVC:52%pred [43–65]). Frailty was observed in 33(37%) patients who were older, had a higher BMI and CCI, more likely to have non-IPF diagnosis, lower 6MWD prior to AE-ILD, and greater dependence for activities of daily living. During hospitalization, a greater proportion of frail patients experienced medical complications (Frail:58%, Non-frail:27%, Table 1) and required greater multidisciplinary support (i.e., occupational therapy, Frail:39%, Non-Frail:16%), $p<0.05$ for all comparisons). No differences were observed in hospital length of stay (Frail: 10days [7–13], Non-Frail: 9days[7–11]), discharge disposition or hospital mortality (Frail:38%, Non-Frail:20%, $p>0.05$).

Conclusion: Frailty in AE-ILD patients is associated with greater physical limitations, multidisciplinary support, and medical complications during hospitalization. This study evaluating the prognostic utility of frailty in AE-ILD patients is ongoing.

Supported by: Canadian Pulmonary Fibrosis Foundation and CIHR (PJM 179846).

Table 1: Clinical characteristics and hospital outcomes

	Frail (n = 33)	**Non-frail (n = 56)**	**p-value**
Population characteristics			
Age, y	70 (64 – 74)	66 (61 – 69)	**0.008**
Sex, n males (%)	19 (58)	35 (63)	0.055
Body mass index, kg/m^2 (n=32; 55)	28.8 (25.5 – 31.3)	25.7 (21.6 – 28.4)	**0.002**
Interstitial lung disease diagnosis, n(%)			**0.004**
Idiopathic lung fibrosis	14 (42)	42 (75)	
Non-Idiopathic lung fibrosis	19 (58)	14 (25)	
Comorbidities, Charlson Comorbidity Index	5 (3 – 6)	3 (2 – 4)	**<0.001**
Pulmonary function			
Forced vital capacity, %pred. (n=29; 41)	54 (44 – 65)	51 (42 – 63)	0.467
Diffusion capacity, % pred.(n=14 ;22)	45 (41.3 – 52.5)	46 (42.0 – 53.5)	0.948
6-minute walk distance, m (n=20; 29)	294 (229 – 380)	396 (315 – 495)	**0.048**
6-minute walk distance, %pred	65.1 (51.0 – 89.9)	81.8 (71.7 – 101.9)	0.110
Dependent in Activities of Daily Living, n(%)			**0.004**
Instrumental activities of daily living	15 (48)	13 (23)	
Basic activities of daily living	8 (26)	8 (14)	
In-hospital clinical outcomes			
Medical complication, n(%)	19 (58)	15 (27)	**0.008**
Hyperglycemia	4 (12)	6 (11)	
Cardiovascular event	4 (12)	2 (4)	
Electrolyte imbalance	2 (6)	3 (5)	
Respiratory etiology	2 (6)	2 (4)	
ICU transfer	2 (6)	1 (2)	
Delirium	2 (6)	0 (0)	
Others$^+$	3 (9)	1 (2)	
Physiotherapy consultation	20 (61)	31 (55)	0.794
Occupational therapy consultation	13 (39)	9 (16)	**0.027**

Data is represented as median (interquartile range), or proportion and percentage, *Data is missing: BMI: n=1 frail patients and n=1 non-frail patients FVC: n=4 frail patients and n=15 non-frail patients, DLCO: n=19 frail patients and n=34 non-frail patients, 6MWD: n=13 frail patients and n=27 non-frail patients. $^+$ Other medical complications were either decubitus ulcer, bacteremia or kidney failure.

Abstract 11:

Positive Airway Pressure Therapy Usage for Obstructive Sleep Apnea in the Lung Transplant Population

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Introduction: There is a high reported prevalence (40%-71%) of obstructive sleep apnea (OSA) in the pre- and post-lung transplant population. While lung transplant is an effective life-saving treatment for lung disease, it does not alleviate pre-existing OSA. Post-lung transplant observational data in those with OSA suggests that positive airway pressure (PAP) usage is associated with lower mortality. Non-adherence to PAP therapy is common in the general population, but has not been evaluated in the transplant population.

Objective: To evaluate PAP usage in the lung transplant population over time.

Methods: This is an exploratory retrospective cohort study of adult lung transplant patients from the University Health Network, Toronto, who received lung transplant between September 1997 and August 2021. Patients with OSA were identified from the lung transplant database. Data on demographics, lung transplant status and outcomes, medical comorbidities, PAP prescription and usage were abstracted from medical records.

Results: A total of ninety-six patients were identified with OSA in both the pre- and post-lung transplant period. The mean (SD) age at transplant was 56.5 (11.6) years and 71.9% were male. 62 patients were diagnosed with OSA pre-transplant and 34 post-transplant. By the last follow-up date, PAP usage was 46.9% (45/96 patients) in post-transplant patients vs. 78.6% (44/56 patients) pre-transplant ($p = 0.0002$). In those who used PAP pre-transplant, 38.6% discontinued post-transplant, despite documented weight gain in 79.2% of patients post-transplant. Baseline apnea hypopnea index (AHI) is significantly higher in those who continued to use PAP post-transplant compared to those who did not (41.5 events/hour vs. 26.6 events/hour, $p = 0.028$).

Conclusion: In the lung transplant population diagnosed with OSA and prescribed PAP therapy, usage significantly declined from the pre- to post-transplant period. This identifies an important gap in the care of post-lung transplant patients, considering that PAP non-adherence has been linked to poorer outcomes in this population.

Abstract 12:

Differences in cardiovascular morbidity and mortality between patients with heart failure with reduced ejection fraction and either obstructive or central sleep apnea

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Introduction: In individuals with heart failure (HF) and reduced ejection fraction (HFrEF), central (CSA) and obstructive sleep apnea (OSA) are associated with increased morbidity and mortality. Previous studies suggest that patients with CSA have more advanced HF than those without CSA, indicating CSA may reflect worse HF. In contrast, there is no such evidence for OSA. ADVENT-HF was a randomized trial that tested the effects of treating OSA and CSA, stratified a priori, with adaptive servo-ventilation (ASV) vs no treatment on morbidity and mortality in patients with HFrEF. However, ASV did not affect prognosis.

Objective: We hypothesized that patients with CSA would have greater morbidity and mortality than those with OSA.

Methods: We performed a post-hoc analysis comparing the incidence of the primary endpoint (composite of all-cause mortality, cardiovascular hospital admissions, new-onset atrial fibrillation , and delivery of an appropriate discharge from an implanted cardioverter-defibrillator) and all cause-mortality between OSA and CSA. Kaplan-Meyer estimates and Cox proportional hazard models were used for analysis.

Results: 731 participants were included, 533 with OSA and 198 with CSA. Compared to OSA, those with CSA were older [median age 68 (interquartile range (IQR) 59-74)] vs [63 IQR (55-59), more likely to be male 95% vs 85%, $p < 0.001$ each, and had a lower left ventricular ejection fraction (LVEF) [33% IQR (25-38)] vs 35% [IQR (28-40), $p=0.011$. As shown in the figure, median time to primary endpoint was 484 days shorter in the CSA than in the OSA group, (1,081 vs 1,565 days: hazard ratio (HR) 1.32, 95% confidence interval (CI) 1.05-1.67, $p=0.017$). For all-cause mortality the HR was higher in CSA: 1.54 (CI 95% 1.09-2.22, $p=0.015$).

Conclusion: Participants with CSA had higher morbidity and mortality than those with OSA. This novel finding may be explained by differences between the groups in age and LVEF.

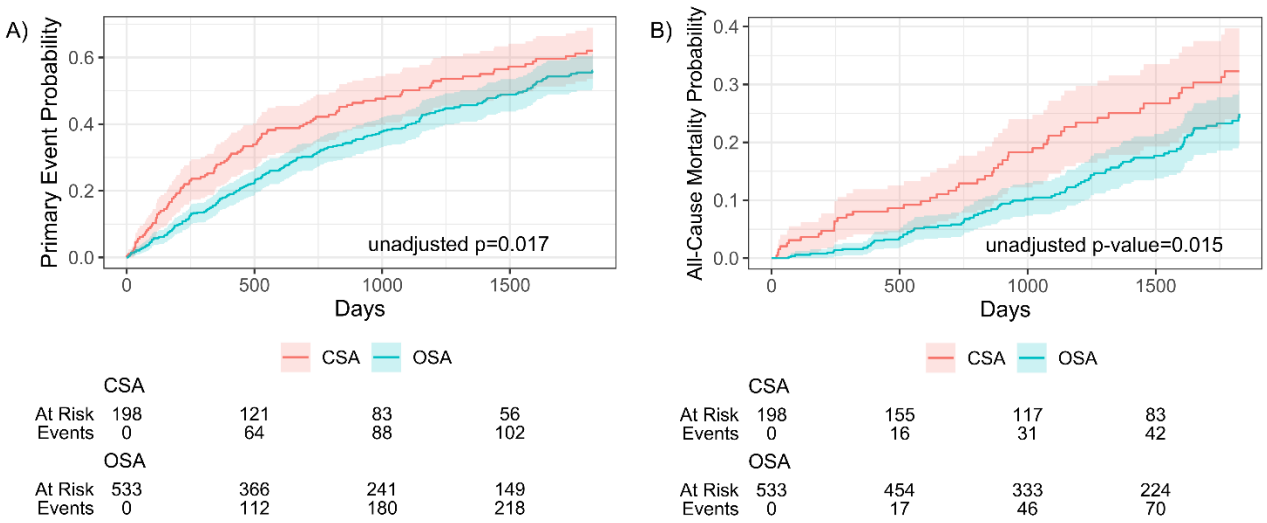

Figure: Kaplan-Meyer estimates

A) Primary event probability: red curve indicates the CSA group, turquois curve indicates the OSA group and toned down colours indicate 95% confidence interval.

B) All-cause mortality probability

Abstract 13:

Investigating the Safety of Tunneled Intraperitoneal Catheters for Palliative Care in Malignant Ascites

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Introduction & Objectives: Malignant ascites can cause severe discomfort, pain, and dyspnea in advanced cancer patients. Tunneled intraperitoneal catheters (TIPC) for recurrent drainage of ascites are commonly used to alleviate these symptoms, but their safety remains uncertain. We aimed to describe the frequency of anticipated complications from TIPC in patients with advanced malignancy at a tertiary care center.

Methods: We conducted a retrospective study of TIPC insertions, outlining the identified complications and their respective rates over a 9-year period at Sunnybrook Health Sciences Centre.

Results: In total, 339 patients who underwent catheter insertion were followed for a mean duration of 92 days after TIPC insertion. The rate of serious complications (peritonitis, acute kidney injury, hypotension) was 11.8%. The overall complication rate, where patients experienced any complication, was 19.8%. Individual complications and their respective rates included acute kidney injury attributable to drainage (5.3%), leakage at the insertion site (6.5%), local infections requiring antibiotics (3.5%), hypotension (2.7%), bacterial peritonitis (2.4%), blockage requiring thrombolytics (0.09%), pain requiring removal (0.06%), and tumour seeding (0.03%). No intra-procedural complications such as major bleeding or visceral injury were reported. TIPCs were removed in 26 patients (7.7%) either due to resolution of ascites or a complication as listed above.

Conclusion: Our findings suggest that TIPCs are a safe tool for symptom relief in patients with malignant ascites. The low rate of complications during catheter insertion and follow-up indicates that TIPCs may be an effective option to alleviate the symptoms of malignant ascites."

Supported by: Division of Respirology, Department of Medicine, University of Toronto

Abstract 14:

Classification of preserved ratio impaired spirometry using oscillometry

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Introduction & Objective: Preserved ratio impaired spirometry [PRISm (spiro)] is a spirometric pattern defined as the reduced forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC), with normal FEV1/FVC ratio. Total lung capacity (TLC) allows classification of PRISm (spiro) into 1) restriction, which is confirmed by a reduced TLC, and 2) true PRISm, which has normal TLC. When TLC is unavailable, it is challenging to differentiate between the two, leading to delayed diagnosis and treatment. We aim to explore whether oscillometry, a pulmonary function modality highly sensitive to lung mechanics, can provide additional information to classify PRISm (spiro) as true PRISm versus restriction in the absence of TLC.

Methods: This retrospective cross-sectional study included 959 patients with valid spirometry, plethysmography and oscillometry data from 2017-2022. Lung function patterns were classified according to ATS and UofT guidelines, and were compared using t test or Mann-Whitney U Test for continuous variables and $\chi 2$ test for categorical variables. A multivariable logistic regression model was applied to classify PRISm (spiro).

Results: Among the 271 identified PRISm (spiro) patients in our study, distinct metrics of pulmonary function and lung mechanics were found in true PRISm (n=26) and restriction (n=245). Compared to restriction, true PRISm had higher lung volume (FVC% predicted=62.05±12.44 vs 73.82±7.82, P<0.001; TLC% predicted=62.37±10.09 vs 89.13±6.87, P<0.001) and greater air trapping (residual volume/TLC=41.2±9.3 vs 45.5±8.3, P=0.024), and higher resistance at 5 Hz (R5) [z scores=0.61 (0.03, 1.22) vs 1.35 (0.72, 1.95), P<0.001] on oscillometry. R5 (OR 3.45, 95% CI 1.28□9.29, P=0.007) was an independent predictor for differentiating true PRISm from restriction, exhibiting a 90.1% accuracy and a 0.904 area under precision-recall curve.

Conclusion: R5 on oscillometry is a particularly valuable characteristic of classifying PRISm (spiro) into true PRISm and restriction when TLC is unavailable."

Support: The research team would like to thank all participants and clinical staffs at the University Health Network in this study. We are also grateful for financial research support by the Lung Health Foundation, Canadian Institutes for Health Research (CIHR; grant number 4518060 and the CIHR-Natural Sciences and Engineering Research Council Collaborative Health Research Programme; grant number 415013) and scholarship support to ZLW by Chinese Scholarship Council.

Abstract 15:

Machine Learning Using MiniRocket Improves the Diagnostic Acumen of Spirometry

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Introduction: Spirometry and plethysmography are the gold standard pulmonary function tests (PFTs) for lung disease diagnosis. Spirometry is often used alone due to inaccessibility of plethysmography, resulting in missed and mis-diagnoses as spirometry alone cannot identify restriction nor early obstruction in small airways. We previously showed that multi-layer perceptron using FVC, FEV1, FEF25-75, sex, age and height classifies normal, obstruction, restriction and mixed obstruction-restriction with higher accuracy compared to respirologists (95% vs. 67%). However, these singular spirometric parameters are limited in detecting early small airway disease. Conversely, spirometry flow-volume loops provide a complete representation of inspiration and expiration, including flow in small airways.

Hypothesis: MiniRocket using the spirometry flow-volume loop can identify obstruction, restriction, mixed obstruction-restriction, and small-airway obstruction.

Methods: 2871 PFTs from 895 patients were labelled as normal, obstruction, restriction, mixed, and SAO according to interpretation guidelines. We built a novel algorithm using cascaded MiniRocket classifiers and loops from the first 774 patients. Loops were first classified as normal vs. abnormal, then obstruction and small-airway obstruction vs. restriction and mixed, and finally obstruction vs. small-airway obstruction, and restriction vs. mixed, each using 80%-20% train-test split. The model was then validated using 2571 PFTs from the first 774 patients for training, and 300 previously unseen PFTs from the next 121 patients in the test set.

Results: Mean accuracies for the cascaded classifiers using spirometry flow-volume loops range from 89-95% (Table 1). Validation with the next 121 patients confirmed similar accuracies (Table 1).

Conclusion: MiniRocket using flow-volume loops classifies the major respiratory patterns including small-airway obstruction and improves diagnostic acumen when only spirometry is available. This has important implications for increasing equitable access to prompt and appropriate management for lung diseases.

Table 1. Mean accuracies for cascaded MiniRocket classifiers using spirometry flow-volume loops as inputs.

Classifier	**2571 PFTs from first 774 patients (80% in training set, 20% in test set) (%)**	**2571 PFTs from first 774 patients in training set, 300 PFTs from next 121 patients in test set (%)**
Normal vs. Abnormal	93.58±0.03	91.22±0.1
[Obstruction and Small-Airway Obstruction] vs. [Restriction and Mixed Obstruction-Restriction]	90.01±0.07	89.28%±0.06
Obstruction vs. Small-Airway Obstruction	88.50±0.03	87.63±0.13
Restriction vs. Mixed Obstruction-Restriction	95.55±0.01	93.89±0.04

Abstract 16:

A Computational Interrogation of the Validity of Activating Neurons as a Test of Their Functional Importance in Sleep-Wake Control Networks

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Background/Rationale: Understanding sleep/wake states of the brain is enabled by demarcation experiments: i.e., experiments that aim to distinguish functionally critical from non-critical neuronal groups. Taken together, they seek to demarcate the minimum set of neuronal groups that need be considered to explain sleep/wake dynamics. Neuronal group/node importance is commonly evaluated by two main strategies: node-by-node activation and inactivation. While these strategies are assumed to be complimentary, it may be argued that neuronal activation yields spurious results. However, the true epistemological validity of activation cannot be empirically determined in vivo. Such an empirical test may be performed computationally, using exhaustive interrogation of simulated networks.

Methods: Candidate networks were generated by randomly varying network parameters. Networks had generalized pareto degree distributions (50-nodes), were weighted log-normally, were signed, and directed. Nodes, representing pools of neurons, had analog I/O, determined by variable sigmoidal activation functions, rates of activity decay, bias and noise. Network fitness was evaluated relative to characteristics attributable to sleep-wake networks: anti-correlated node clusters, state bistability, state rebound after 'deprivation'. Network fitness was further optimized using a genetic algorithm.

Results: For each network (n=31), exhaustive node-by-node activation and inactivation experiments were performed (n=3100). The effect sizes were compiled into activation and inactivation-based ordinal node-importance rankings. Ranking validity was tested with a network-attack approach where progressively larger groups of nodes were removed, moving from the least important to the set of 25 least important. A similar set of simulated experiments were performed on an edge-by-edge basis (n~100,812). Rankings generated by a valid epistemological process will affect network dynamics less compared to random rankings.

Conclusion: While inactivation-based rankings outperformed randomized rankings in preserving network dynamics, the performance of activation was equivalent to randomly guessing. This data does not support the validity of neuronal activation as a means of demarcating functionally important nodes in sleep-wake networks.

Abstract 17:

Palliative care and symptom burden among lung cancer patients with and without COPD: A population-based cohort study

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Introduction & Objectives: Lung cancer patients with chronic obstructive pulmonary disease (COPD) may have greater palliative care needs due to poor prognosis and symptom burden. We sought to compare the provision of timely palliative care and symptom burden by COPD status.

Methods: We performed a retrospective, population-based cohort study of lung cancer patients diagnosed between January 1st 2009 and March 31st 2019, using health administrative databases and cancer registries. Participants were followed until death or a maximum follow-up date of March 31st 2020. The impact of COPD on the probability of receiving palliative care was determined accounting for dying as a competing event, with an overall analysis and stratification by stage of lung cancer. The provision of palliative care for patients with severe symptoms (Edmonton Symptom Assessment Scale score = 7 or higher), location of the first palliative care visit, and symptom severity, were also compared by COPD status.

Results: 74,993 lung cancer patients were included in the study and symptom data was available for 48% of patients. At the time of lung cancer diagnosis, 50% of patients had COPD. Early-stage patients were more likely to receive palliative care if they had COPD (Stage I adjusted Hazard Ratio (HR) (95% CI): 1.31 (1.25 to 1.38)). In the advanced stages, there was no significant difference in receipt of palliative care by COPD status. Despite having severe symptoms, very few patients with early-stage lung cancer received palliative care (Stage I: COPD-23% vs. no COPD-18%, SMD=0.12). Most patients (84%) reported severe symptoms and COPD worsened symptom burden, especially among patients with early-stage disease.

Conclusion: COPD impacts the receipt of palliative care and symptom burden for patients with early-stage lung cancer. Many patients with severe symptoms did not receive palliative care, suggesting unmet needs among this vulnerable population.

Supported by: Division of Respirology, Department of Medicine, University of Toronto

Abstract 18:

Does Inspiratory Muscle Loading and Associated Dyspnea Affect Visual Attention?

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Affiliations: 1. Department of Physical Therapy, University of Toronto, Toronto, ON, Canada, 2. Division of Respirology & Lung Transplant Program, University of Toronto & University Health Network, Toronto, ON, Canada,

Introduction & Objectives: This study investigated the impact of dyspnea induced by inspiratory muscle loading on cognitive performance in healthy individuals. Previous studies have shown that dyspnea induced with inspiratory muscle loading can impair various cognitive functions but none of these examined the effect of dyspnea on visual attention. The purpose of this study was to compare accuracy of a visual attention single task to dual-tasks when the visual attention task was combined with low and moderate inspiratory threshold loads (ITL).

Methods: Twenty-five healthy adults (24.3+ 2.4 yr; 18F:7M) were tested. Visual attention was quantified using a multiple object tracking (MOT) test, and dyspnea was induced using ITL at a low 20 cmH2O (ITL20) or a moderate 40 cmH2O load (ITL40). Participants performed single and dual tasks in random order: 1) single-task: MOT; 2) single-task: ITL20; 3) single-task: ITL40; 4) dual-task: MOT+ITL20; 5) dual-task: MOT+ITL40. Ventilatory measures (RR, mouth pressure, tidal volume, end-tidal CO2), perceived levels of dyspnea (Borg), and emotional impact (Self-assessment manikin) of the single and dual task ITL were also measured.

Results: The highest level of accuracy was achieved by the single task MOT and MOT accuracy was significantly lower during MOT+ITL20 ($p=0.007$) and MOT+ITL40 ($p=0.001$) (Figure). Even the accuracy during MOT+ITL40 was lower than MOT+ITL20 ($p=0.009$). Further, the accuracy of MOT during dual task MOT+ITL20 was correlated with maximal inspiratory pressures at $r=.465$ ($p=0.01$); maximal inspiratory pressure versus MOT+ITL40 was also correlated at $r=.464$ ($p=0.01$).

Conclusion: Individuals undergoing ITL and associated dyspnea have decreased performance on a visual attention task. The accuracy of attending to this visual task was related to maximal inspiratory muscle strength. Whether this visual attention test can detect cognitive interference in patients experiencing dyspnea is worthy of exploration. Further its responsiveness to change after therapeutic interventions could be investigated.

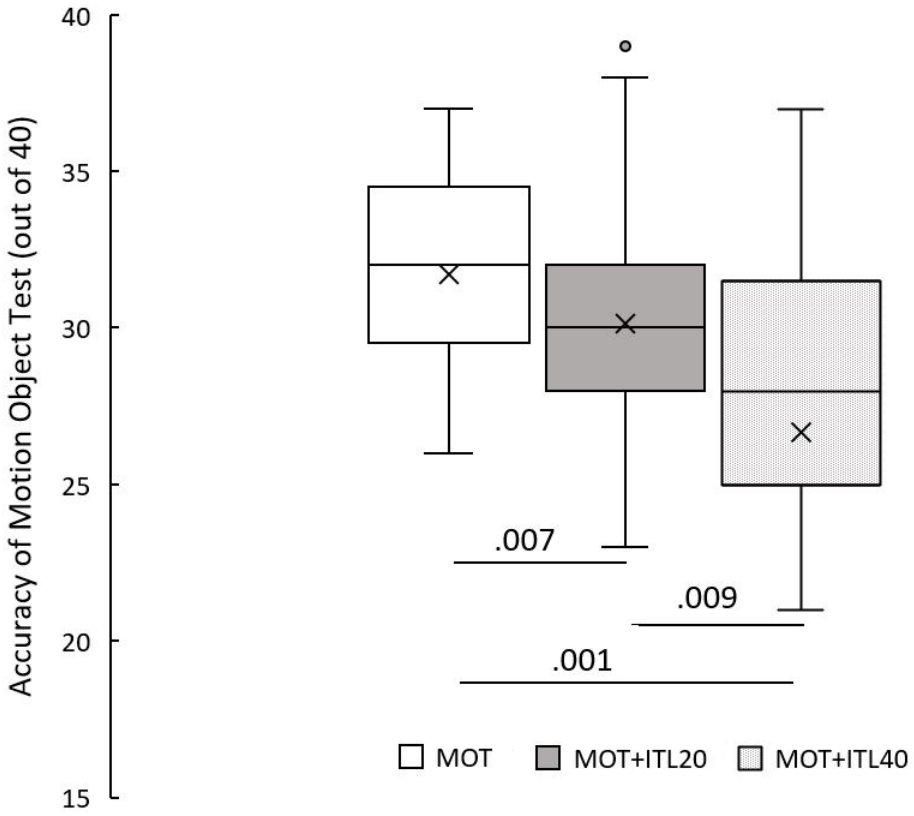

Figure: The highest level of accuracy was achieved by the single task MOT and MOT accuracy was significantly lower during MOT+ITL20 (p=0.007) and MOT+ITL40 (p=0.001)

Abstract 19:

Real-world impact of elexacaftor/tezacaftor/ivacaftor on quality of life for adults with Cystic Fibrosis.

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1. Divison of Respirology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada. 2. Toronto Adult Cystic Fibrosis Centre, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada.

Introduction: Clinical trials have shown that elexacaftor/tezacaftor/ivacaftor (ETI) improves clinical outcomes in people with Cystic Fibrosis (pwCF). Trials have also reported improved scores on the respiratory domain (RD) of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), however this may not represent real-world outcomes. We aim to investigate this real-world effect on health-related quality of life (HRQoL) by analyzing the change in the scores of validated questionnaires after starting treatment.

Methods: This is a prospective cohort study of pwCF who received ETI between June 2021-March 2023. Participants completed 3 questionnaires (CFQ-R, CF QoL Evaluative Self-administered Test (CF-QUEST), and 22-Item Sinonasal Outcome Test (SNOT-22) prior to starting ETI and at prespecified intervals afterwards. Each domain of CFQ-R and CF-QUEST is scored 0-100 (higher score indicating higher HRQoL). The minimal clinically important difference (MCID) for the CFQ-R RD is 4-points. The SNOT-22 assesses the impact of rhinosinusitis (scored 0-110, higher scores indicating worse HRQoL). Clinical characteristics within 30 days prior to each questionnaire were summarized from the Canadian CF registry. Generalized estimating equations were used to compare the scores at each time interval.

Results: A total of 96 patients were included with a median age of 30.4 years. Median ppFEV1 at baseline was 67.9 (IQR 56.1-77.5) which increased to 78.7 (IQR 69.1-92) at 3 months. Baseline BMI was 21.8 (IQR 20.3-24.4) kg/m2 which increased to 23.5 (IQR 21.8-25.3) at 3 months. Scores for all domains of the CFQ-R and CF-QUEST increased from baseline to 3 months ($p<0.05$). The CFQ-R RD was 66.7 (IQR 44.4-77.8) at baseline increasing to 94.4 (IQR 83.3-100) at 3 months ($p<0.001$). SNOT-22 score decreased by 15.8 points (IQR 12.1-19.5) after 3 months ($p<0.001$).

Conclusions: Our study demonstrates that ETI significantly improved HRQoL for pwCF in the real world setting. The improvement in CFQ-R RD exceeded that previously published in clinical trials."

Abstract: 20

Influence of pulmonary rehabilitation on symptoms of anxiety and depression in interstitial lung disease: A systematic review of randomized controlled trials

Brandon Luu MD (1)*, Nicholas Fabiano MD (2)*, Arnav Gupta BHSc (3,4), Stanley Wong MD (5), Jess G Fiedorowicz MD PhD (2,6,7,8), Lee Fidler MD MSc (9), Risa Shorr MLS (10), Marco Solmi MD PhD (2,6,7,8)

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Introduction & Objectives: Interstitial lung diseases (ILD) are a group of disorders characterized by progressive fibrosis of the lung, contributing to dyspnea, functional decline, and impaired quality of life. Individuals with ILD also experience a high prevalence of symptoms of anxiety and depression. Studies have demonstrated a benefit of pulmonary rehabilitation in alleviating symptoms of anxiety and depression in patients with Chronic Obstructive Pulmonary Disease (COPD). However, there is a lack of synthesized data on the effect of pulmonary rehabilitation on symptoms of anxiety or depression in those with ILD.

Methods: We conducted a systematic review adhering to PRISMA 2020 guidelines searching MEDLINE, EMBASE, Cochrane, and PsycINFO for randomized controlled trials investigating the effect of pulmonary rehabilitation on symptoms of anxiety and depression in patients with ILD. We used the Cochrane Risk of Bias 2 tool for quality assessment.

Results: Of 1334 eligible studies, six studies (n=332) were included. Idiopathic pulmonary fibrosis (IPF) was the most commonly included type of ILD (k=3). Most studies used a combination of aerobic and strength-based pulmonary rehabilitation (k=5). One study found a statistically significant reduction in anxiety following pulmonary rehabilitation, however the remainder (k=5) found no significant change. All studies (k=6) found no statistically significant change in depression after pulmonary rehabilitation. There was no apparent difference in dropouts in those randomized to pulmonary rehabilitation versus control conditions.

Conclusion: Our systematic review did not observe a statistically significant change in symptoms of anxiety or depression following pulmonary rehabilitation in people with ILD relative to control groups. Randomized controlled trials with larger sample sizes, more standardized scales measuring anxiety and depression, consistent time-point measurements, and subgroup analyses are required to better understand these associations. Further research should also explore other strategies to improve symptoms of anxiety and depression in patients with ILD."

Supported by: Department of Psychiatry, University of Ottawa, Ottawa, and Division of Respirology, Department of Medicine, University of Toronto.

Abstract 21:

Clinical Implications of Exercise Capacity at 3-months Post Lung Transplantation on 5-Year Outcomes

Mohamed Khalil (1), Jeff Park (1), Sahar Nourouzpour (2), Tereza Martinu (1,2), & Dmitry Rozenberg (1,2)

1)Temerty Faculty of Medicine, Division of Respirology, University of Toronto 2) Respirology and Lung Transplantation, Ajmera Transplant Program, Toronto General Hospital Research Institute, University Health Network, Toronto

Background: Hospitalizations are common post lung transplantation (LTx) and associated with increased morbidity and mortality. The use of six-minute walk distance (6MWD) as a prognostic physiologic marker for postoperative outcomes in LTx recipients has not been commonly utilized. The aim of this study is to assess the prognostic utility of exercise capacity at 3-months post-LTx as a predictor of all-cause hospital admissions, chronic lung allograft dysfunction (CLAD) and post-transplant survival over a 5-year period.

Methods: Single center retrospective cohort study of 144 consecutive adult LTx recipients listed in 2014/15 in the Toronto LTx Program. Clinical demographics, 6MWD, hospital admissions, CLAD and 5 year-survival were abstracted. Given no established cut-offs for low 6MWD at 3-months post-transplantation (primary exposure variable), the lowest quartile (Q1) was used to define low exercise capacity compared to the other three quartiles (Q2-Q4). T-tests and chi-squared tests were use to compare clinical characteristics and outcomes between two groups (Q1 versus Q2-Q4 exercise capacity).

Results: Of the 144 LTx recipients, mean age was 54 ± 13 years, 60% were male, with majority transplanted for ILD (51%) or COPD (23%), with no differences in age, sex or diagnosis. Over a 5-year period, Q1 demonstrated increased median number of admissions (Q1: 1.4 IQR [0.6 to 2]vs. Q2-Q4 0.6 [0.2 to 1.6] per year, p=0.002). The two most common causes for hospital admissions were respiratory related admission (44%) and gastrointestinal etiologies (13%). Chronic allograft dysfunction over 5-years was observed in 42% with no difference between the two groups (p=0.61). The five-year mortality was higher in Q1 compared to Q2-Q4 ((49% vs. 28%, p=0.02).

Conclusion: Results highlight that exercise capacity at 3-months post-transplant may be an important marker of hospital readmissions and mortality. Rehabilitation interventions that improve exercise capacity post-transplant may influence morbidity and mortality.

Key words: Exercise Capacity •Post Lung Transplantation • Hospital Readmission •Survival"

Supported by: Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine.

Abstract 22:

Trends in Prevalence of Chronic Obstructive Pulmonary Disease in Immigrants to Ontario, Canada, 2002-2019.

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Introduction & Objectives: Between 2010-2019, Canada welcomed nearly 2.8 million immigrants and refugees, with nearly 50% settling in Ontario. The burden of COPD among this population is poorly understood. We aimed to determine prevalence and trends in prevalence of COPD among immigrants to Ontario compared to non-immigrants.

Methods: We conducted a population-based cross-sectional study of immigrants to Ontario between April 1, 2002 and March 30, 2020 using health administrative databases. The primary outcome was COPD prevalence, ascertained using a validated algorithm. The primary exposure was immigrant status, categorized as non-immigrants, immigrant < 5 years, 5-14 years, or 15 years. Poisson GEE regression was used to estimate the association between prevalence of COPD and immigrant status, compared to non-immigrants, after adjustment for age, sex, rurality, neighbourhood income and year.

Results: In Ontario, there were 1,738,748 (23% of Ontario population) immigrants between April 1, 2002 and March 30, 2020. In 2019, crude COPD prevalence was 2.0%, 3.4%, 6.8% in immigrants < 5 years, 5-14 years, and ≥ 15 years, respectively, in comparison to 14.1% in non-immigrants. The prevalence of COPD increased in non-immigrants, but was relatively stable in immigrant groups 0-14 years post-immigration. In adjusted analysis, immigrants < 5 years, 5-14 years, and ≥ 15 years had rate ratios of having COPD compared to non-immigrants of 0.24 (95% CI 0.24-0.24), 0.46 (95% CI 0.45-0.46), and 0.66 (95% CI 0.65-0.66), respectively.

Discussion: The prevalence of COPD is lower among immigrants compared to non-immigrants, and has remained stable compared to non-immigrants over time. Similarly, immigrants carry a lower risk of COPD compared to non-immigrants. This may be explained by the “healthy immigrant effect”, where immigrants may be generally healthier and younger than local-born individuals. Additionally, COPD may be under-diagnosed or under-reported in immigrants due to structural barriers to accessing healthcare services."

Abstract 23:

Respiratory Oscillometry for Early Diagnosis of Chronic Lung Allograft Dysfunction

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

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, ON, Canada. 3Pulmonary Function Laboratory, University Health Network. 4. Department of Anesthesiology and Intensive Therapy, Semmelweis University.

Background: Chronic lung allograft dysfunction (CLAD) is the main obstacle to long-term survival after lung transplantation (LTx). CLAD is suspected when the forced expiratory volume in 1 second (FEV1) falls to ≤ 80% of the baseline value but is not confirmed until it is sustained for at least 3 months and other causes are ruled out. Oscillometry (Osc) is a highly sensitive pulmonary function test (PFT) modality. The current study investigated whether Osc can differentiate between LTx patients who will recover or develop CLAD at the initial ≥20% drop in FEV1.

Methods: A retrospective, cross-sectional analysis of 397 double LTx recipients enrolled between December 2017 and January 2023 was conducted. Patients who experienced a ≥20% drop in FEV1 but then recovered (noCLADdrop, n=25) and those who subsequently developed CLAD (n=52) were time-matched to patients who have not experienced a drop in FEV1 (CLAD-free, n=320) but had PFTs within 2 weeks of the respective FEV1 drop dates. Pairwise comparisons between groups were performed with Wilcoxon tests followed by Bonferroni correction.

Findings: At the initial ≥20% drop in FEV1, CLAD-free patients had significantly better spirometry and spectral Osc than both noCLADdrop and CLAD subjects. While spirometry was unable to distinguish between noCLADdrop and CLAD patients, the spectral Osc metric reactance at 5 Hz (X5) was significantly worse in the CLAD patients ($P = 0.0175$).

Conclusions: Spectral Osc, specifically X5, was able to differentiate patients that will recover or go on to develop CLAD at the initial drop in FEV1. X5 is a biomarker that could be used for early confirmation of CLAD."

Support: The study was funded by the CIHR-NSERC Collaborative Health Research Projects, the Peterborough K.M. Hunter Charitable Foundation Graduate Award (AF), and the CLA and CIHR-ICRH Research Studentship (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 24:

The impact of COVID-19 on lung function in cystic fibrosis: A global observational study

Julie Semenchuk (1), Yumi Naito (2), Susan Charman (2), Stephanie Cheng (3), Anne Stephenson (1), on behalf of the Cystic Fibrosis Registry Global Collaboration 1. Division of Respirology, St. Michael's Hospital, University of Toronto, ON, CA. 2. Cystic Fibrosis Trust, London, UK. 3. Cystic Fibrosis Canada, Toronto, ON, CA.

Introduction & Objectives: The cystic fibrosis (CF) community has well-established patient registries around the world. Through the development of a novel global CF data collection process, we aimed to determine the impact of COVID-19 infection on lung function.

Methods: This is a retrospective cohort study of individuals with CF with confirmed COVID-19 infection diagnosed by PCR or rapid antigen testing between January 1, 2020 and December 31, 2021. At the onset of the pandemic, members of the CF Registry Global Collaboration convened regular meetings to discuss how to aggregate data on this emerging infection. National CF registries were utilized to capture data on confirmed cases and countries without well-established registries submitted data by standardized excel forms or via a newly created REDCap database. Baseline characteristics defined at diagnosis of COVID-19 were recorded. Forced expiratory volume in one second percent predicted (ppFEV1) prior to and following a diagnosis of COVID-19 were obtained.

Results: A total of 7,120 primary COVID-19 infections were identified from 47 countries. The median age at infection was 22 years (IQR 14-32) and 50% were male. 23% had CF-related diabetes, 68% were pancreatic insufficient, and 47% had P. aeruginosa infection. 38% were not on modulators, 12% were non-white, and 82% had at least 1 copy of the F508del mutation. Preliminary analyses reveal 4,050 cases available for ppFEV1 analyses. The median ppFEV1 prior to infection was 83.0 (IQR 62.2-97.1) compared to 83.1 (IQR 63.0-98.5) following infection. The proportion of people with severe, moderate, and mild lung disease was similar pre- and post-infection. Analyses evaluating the impact on rate of decline in ppFEV1 is ongoing.

Conclusions: This work highlights the ability of the global CF community to unify and address critical issues facing people with CF in a timely manner. Preliminary analyses suggest minimal impact on lung function following COVID-19.

Support: Canadian Institutes for Health Research (GA4-177734)

Abstract 25:

Regulatory T Cells In Chronically Rejected Human Lung Allografts Exhibit A Gene Expression Program Suggesting Dysfunction

K. F. Bei, A. Duong, S. Moshkelgosha, T. Martinu, S. Juvet

University Health Network

Introduction: Lung transplant is the only life-prolonging treatment option for end-stage lung disease. Unfortunately, the 10-year survival following lung transplantation is only 32%. One approach to controlling alloimmunity is utilizing regulatory T cells (Tregs) - which are a subset of CD4+ T cells expressing FOXP3 transcription factor; that maintain immune homeostasis and prevent autoimmunity. Our lab has explored directed allograft occupancy by expanded Tregs in a rat model via pre-transplant administration to ex vivo perfused donor lungs. On the other hand, impaired regulation by Tregs in the rejecting allograft may result from altered Treg gene expression and instability, and the long-term persistence and stability of intragraft Tregs is unknown. We hypothesized that chronic lung allograft dysfunction (CLAD) drives changes in intragraft Treg gene expression.

Methods: We generated 3' and T- and B cell-enriched 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). Tregs were identified as cells with 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 0.5.

Results: Comparison of CLAD lung and paired PBMC cells found that RBPJ, SRGN, BATF, TNFRSF4 (OX40, negative regulator of Tregs), and TNGFRSF18 (GITR, function-associated marker) were expressed higher in lung Tregs compared to PBMC Tregs. JUNB (AP-1 pathway of Treg function) was downregulated in CLAD 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.

Conclusions: The downregulation of JUNB, a component of the AP-1 pathway shown in murine studies to be required for efficient Treg function coupled with increased expression of TNFRSF4 (OX40), a costimulatory molecule that inhibits FOXP3 expression suggests dysfunction. In contrast the higher expression of TNFRSF18 (GITR), a function-associated marker relating to Treg proliferation and maturation was found to be higher in lung Tregs. This suggests a dynamic balance between factors promoting Treg function and those driving dysfunction. Further exploration and validation of these findings is underway."

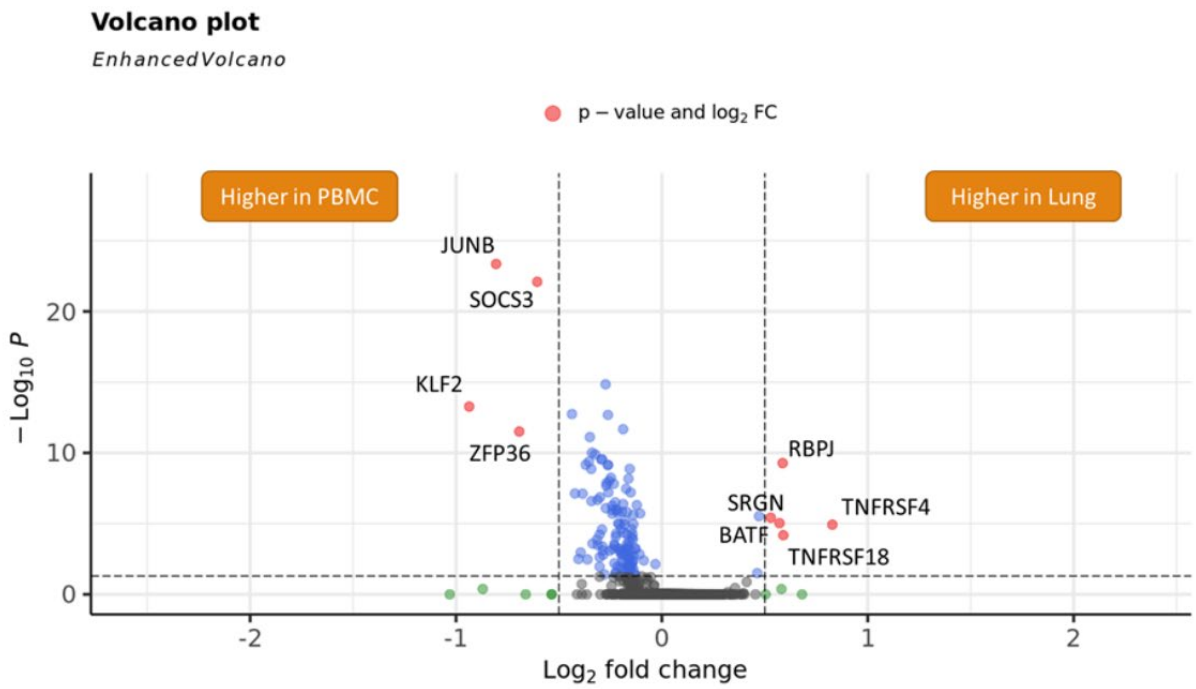

Figure: Differential gene expression of CLAD Lung Tregs vs. matched PBMC Tregs Volcano plot depicting DESeq2 analysis of Tregs in CLAD lung (right) compared withc matched PBMC (left). JUNB and SOCS3 transcripts were elevated in PBMC Tregs, while TNFRSF4 (OX40) and TNFRSF18 (GITR) had higher expression in CLAD lung Tregs. Data analysed via Seurat by R. p-value < 0.05 and log2 fold-change cut-off of 0.5.

Abstract 26:

Timing of Respiratory Muscle Activity during Incremental Inspiratory Loading in Healthy Adults

Umi Matsumura (1, 2), Antenor Rodrigues (3), Kazuya Shingai (1, 2, 4), Peter Rassam (1), Marine Van Hollebeke (1), Tamires Mori (1), Dmitry Rozenberg (4, 5), Laurent Brochard (3, 6, 7), Ewan C Goligher (3, 6, 8), W Darlene Reid (1, 8, 9)

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Background: The timing of the respiratory muscles activity during incremental inspiratory threshold loading (ITL) has not been investigated. We aimed to evaluate the timing of respiratory muscles activity during incremental ITL to task failure in healthy adults.

Methods: Twelve healthy adults (6 female; 29.5±7.1 yrs, maximum inspiratory pressure 118±61 cmH2O) performed an incremental ITL starting low loads (7.6±1.8 cmH2O) then 50g increments every two minutes up to task failure. Surface electromyography (sEMG) on the right hemithorax of costal diaphragm/7th intercostal (diaphragm), scalene, parasternal intercostal, and sternocleidomastoid on the right hemithorax were measured. The root mean square (RMS) and timing (onset, offset and duration of activity) of sEMG for each muscle were quantified throughout the ITL test with a previously validated algorithm (PMID: 35046839). The RMS and timing of sEMG for each muscle were compared at every ITL increment, up to isoload (the maximum load completed by all participants) and task failure (each participant's highest completed load).

Results: Sternocleidomastoid activated earlier at isoload and task failure compared to low loads ($p < 0.015$ respectively) (Figure 1). Scalene and parasternal intercostal activated earlier at task failure compared to low loads ($p < 0.012$ respectively) (Figure 1). Duration of scalene activity increased in the isoload compared to low loads (mean ± standard error [sec] 0.83 ± 0.19, $p < 0.025$). The RMS of scalene, parasternal intercostal, and sternocleidomastoid increased at isoload ($p < 0.02$) and task failure ($p < 0.006$) compared to low loads. Timing and RMS changes of diaphragm were stable during ITL.

Conclusion: With increasing loads, accessory muscles act as a reservoir and their magnitudes increase in healthy adults. Characterizing the respiratory muscle timing during inspiratory muscle loading would provide a foundation for future studies to investigate the effect of age or disease that may contribute to ventilatory limitations.

Support: Funds to perform this study were provided by an NIH grant, UM were funded by Mitacs, MVH by CIHR, and KS and PR by the RAMP Trust fund.

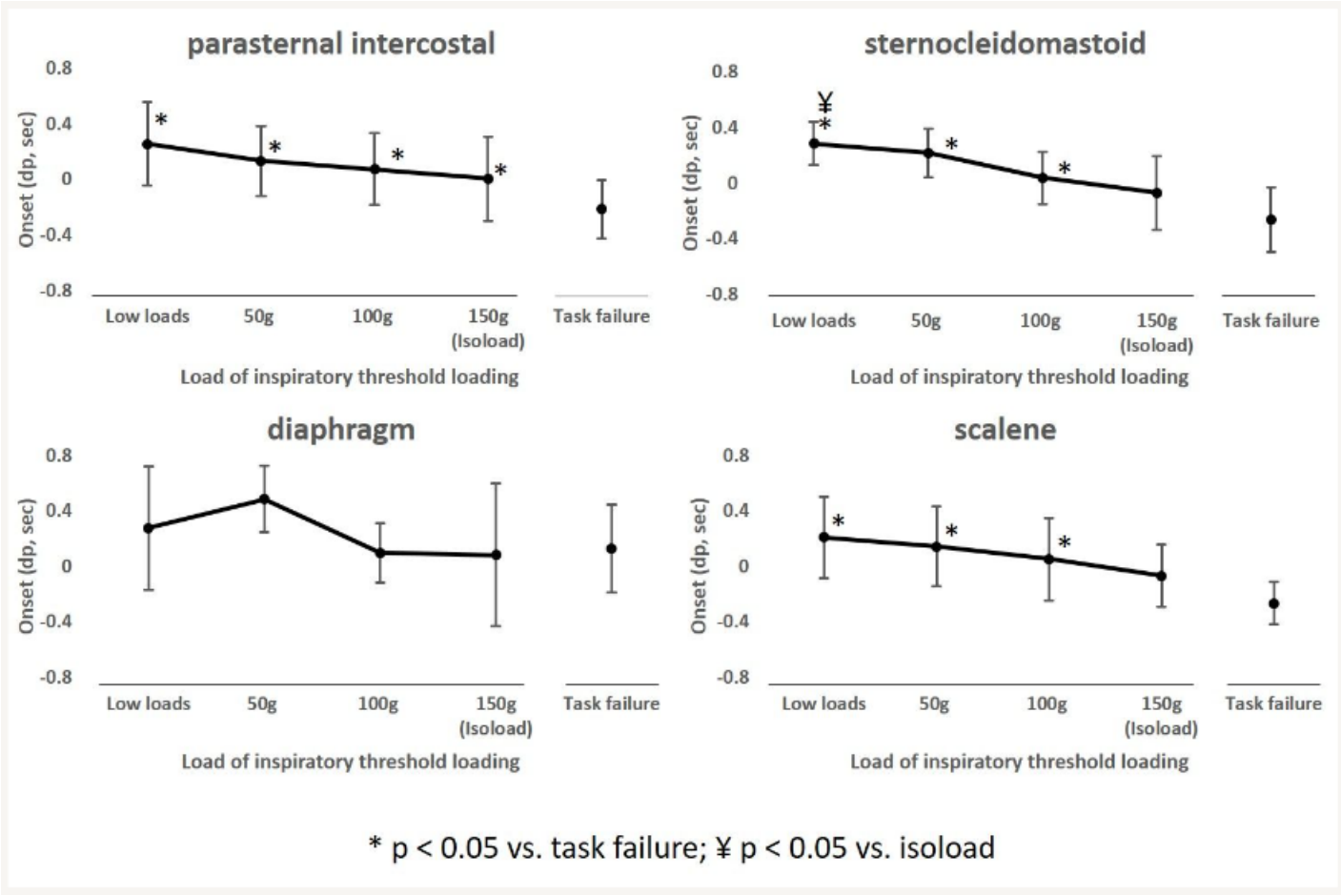

Figure: Illustration of muscle activation of respiratory muscles.

Abstract 27:

Optical interrogation of cholinergic and glutamatergic pre-motor inputs to a medullary circuit essential to rhythmic breathing

Raina Ladha (1), Wenying Liu (1), Hattie Liu (2), Richard Horner (1,2)

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Rationale: Rhythmic motor drive to the upper airway muscles functions to maintain an open airway for effective breathing. This function is compromised by reductions in motor drive during sleep and fails in sleep apnea. The hypoglossal motor nucleus (HMN) is the core of this circuitry but controlling mechanisms have not been identified in-vivo. Hypothesis: We hypothesize that cholinergic and glutamatergic pre-motor inputs to the HMN control endogenous rhythmic motor output during breathing and behavior.

Methods: We optically stimulate (10Hz or continuously for 2s, 0-20mW) light-sensitive cation channels on cholinergic and glutamatergic neurons in isoflurane-anesthetized transgenic mice (ChAT-ChR2-EYFP and VGLUT-ChR2-YFP respectively). Stimuli are applied at the HMN and the intermediate reticular nucleus (IRt), the IRt being the largest source of glutamatergic and cholinergic inputs to the HMN driving respiratory activity.

Results: For the first time in-vivo we identify HMN output responses to optical stimulation of cholinergic neurons at the HMN are larger than at the IRt (n=15, $P<0.001$; e.g., 321% and 216% at 5 and 20mW). HMN output responses to stimulation of glutamatergic terminals at the HMN and IRt neurons were similar (n=4, P=0.077) but >6x larger than cholinergic responses at 5mW. In ChAT-ChR2 mice, optical stimulation at the HMN and IRt also increased tongue respiratory activity at ≥3mW and ≥10mW, respectively (n=5, P=0.018). In VGLUT-ChR2 mice, optical stimulation between breaths increased tonic tongue activity at powers ≥1mW regardless of location (n=4, P=0.003).

Discussion and Future Directions: In-vitro evidence identifies cholinergic inputs to the HMN alter the gain of responses to glutamatergic inputs involved in breathing. Using a combination of microdialysis perfusion and optical stimulation, we will test if this interaction occurs in-vivo to explain: (i) modulation of tonic and respiratory hypoglossal motor activity during breathing, and (ii) the marked reductions in activity that occur in rapid-eye-movement sleep.

Abstract 28:

Machine Learning Can Predict Patterns of Pulmonary Function from Airway Impedance

Michael Tisi; Joyce Wu; Zoltán Hantos; Shahrokh Valaee; Chung-Wai Chow

Division of Respirology, Department of Medicine, University of Toronto, Toronto, Canada; Institute of Biomedical Engineering, Faculty of Applied Sciences and Engineering, University of Toronto, Toronto, Canada; Toronto General - Pulmonary Function Laboratory, University Health Network, Toronto, Canada; Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary; The Edward S. Rogers Sr. Department of Electrical and Computer Engineering, Faculty of Applied Sciences and Engineering, University of Toronto, Toronto, Canada.

Background: Respiratory oscillometry (Osc) is pulmonary function (PF) modality that measures respiratory mechanics; however, interpretation of Osc is challenging.

Hypothesis: Machine learning (ML) facilitates Osc interpretation.

Objective: To develop a novel ML architecture capable of classifying normal (N), restrictive (R), obstructive (O), and mixed O-R patterns of PF and compare its accuracy to expert opinion and a physician verified label.

Methods: Data were taken from 245 subjects with 1924 valid 10 Hz mono-frequency Osc tests. Full PF tests and clinical data were used for the gold standard label. Osc measurements of flow, volume, and pressure were inputted for ML and randomly partitioned into training and validation (70:30) sets based on unique subject count. The MiniROCKET algorithm was applied to generate features from the input data which were resolved by a ridge regression classifier to different patterns of PF. A soft voting scheme was implemented on the output classifier scores to reach a final prediction for each Osc test. Results were averaged over 10 experimental runs. ML performance was compared to 12 experts in the interpretations of 72 randomly selected oscillograms. p-values computed via a two sample T-test were used to indicate the statistical similarity between ML predictions and expert evaluations.

Results: Validation accuracy of ML was 88±3% overall, with highest accuracy in identifying N and R patterns (93±3%). ML was significantly better than expert interpretations of 72 Osc tests for recognizing all patterns ($p<0.001$). A summary of results for the ML architecture and expert interpretations is given below.

Pattern	ML (n=10) [%]	Expert (n=12) [%]	p-value
N	100±0	84±12	<0.001
R	87±2	38±10	<0.001
O	93±13	56±21	<0.001
Mixed O-R	71±2	13±15	<0.001

Conclusions: ML can resolve mono-frequency Osc recordings to N, R, O, and mixed O-R patterns with significantly greater accuracy than experts in the field."

The study was funded by CIHR-NSERC Collaborative Health Research Projects Fund # 506900, 506871.

Abstract 29:

Changing demographics of individuals with Cystic Fibrosis transitioning from pediatric to adult care

Abarnaa Illango (1,2), Xiayi Ma (1), Elizabeth Tullis (1), Anne Stephenson (1)

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Introduction & Objective: The transition from pediatric to adult care can be challenging and with evolving standards of care, the characteristics of young individuals are changing. Widespread use of eradication protocols for chronic infections and annual co-morbidities screenings has changed disease severity which has implications for adult care teams. Our study aims to describe characteristics of people with Cystic Fibrosis (pwCF) during the transition to adult care.

Methods: This retrospective cross-sectional study included pwCF followed at the Toronto Adult CF Program, divided into 3 time-windows (TWs) based on the year they turned 19 years-old (1990-1999, 2000-2009, 2010-2022). Patient-level demographics (i.e. sex, genotype) were described. Clinical variables were collected from between the ages of 18-20, excluding data post-lung transplant. Chi-squared test and logistic regression analysis was used for categorical variables and Kruskal-Wallis test and linear regression analysis for continuous.

Results: A total of 721 pwCF turned 19 years old. The percentage of White pwCF decreased from 97.5% to 92.6%. The female-to-male ratio in the recent TW was higher ($p=0.01$). The prevalence of CF-related diabetes (CFRD) increased from 7.4% (1990-1999 TW) to 22.3% (2010-2022 TW) ($p<0.05$). Mean ppFEV1 increased from 67.0% to 72.4% ($p<0.001$). Regarding disease severity, the proportion with severe and moderate lung disease decreased whereas mild disease increased ($p<0.01$). There was no difference in mean BMI over time. There was a 57% reduction in the risk of having Pseudomonas aeruginosa (PsA) (OR 0.43, 95% CI 0.28, 0.63) and 78% reduction in Burkholderia cepacia complex (OR 0.22, 95% CI 0.13, 0.35).

Conclusion: Over the last several decades, lung health has improved during transition. With fewer individuals having PsA, adult care teams must develop efficient processes to identify new acquisition of PsA. The number of pwCF transitioning with CFRD is notable and requires expertise in diabetes management in the CF team."

Abstract 30:

Lung function decline is mitigated following liver transplantation in people with cystic fibrosis: a retrospective cohort study

Faisal Albaiz (1), Ramos Kathleen (2), Jenna Sykes (1), Sanja Stanojevic (3), Xiayi Ma (1), Bradley Quon (4), Bruce Marshall (5), Elizabeth Cromwell (5), Josh Ostrenga (5), Albert Faro (5), Alexander Albert (5), Chris Goss (2), Anne Stephenson (1).

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INTRODUCTION & OBJECTIVES: Cystic fibrosis (CF) liver disease affects 10% of people with CF (pwCF) with 5% experiencing severe cirrhosis and portal hypertension. With chronic lung infections in pwCF, immunosuppression following liver transplantation (LT) may have a negative impact on lung function. We aim to evaluate health outcomes and survival following LT in pwCF.

METHODS: We performed a retrospective cohort study of pwCF who underwent LT between 1987 and 2019 in the US and Canada. Data sources were from the Canadian and US CF registry after linking it to Organ Procurement and Transplantation Network. Simultaneous lung-liver transplants and individuals who had lung transplant prior to LT were excluded. We analyzed pre- and post-LT percent predicted forced expiratory volume in 1 second (ppFEV1), body mass index (BMI), rates of pulmonary exacerbation (PEx), and overall survival post-LT. A sensitivity survival analysis was performed by lung function.

RESULTS: A total of 402 LT recipients were included. The median age of transplant was 14.9 years and 69.7% of transplants were performed in children less than 18 years old. The rate of decline in ppFEV1 was attenuated after LT from -2.2% predicted per year to -0.7% predicted per year (95% CI -1.2, -0.1; $p<0.001$). Following LT, the rate of decline in BMI was reduced, and there were fewer PEx (0.59 pre vs. 0.39 post; RR 0.65, $p<0.01$). The median survival time post-transplant was 13.7 years and the overall probability of survival at five years was 77.3%. Those with higher lung function pre-LT had a lower risk of death post-LT, and those with genotypes other than F508 deletion had worse survival.

CONCLUSION: LT in pwCF occurs most often in children and is associated with a slower rate of decline in lung function and nutritional status, and a reduction in PEx."

Support: This work was funded by the US CFF; We would like to acknowledge the involvement and continued participation of those living with cystic fibrosis who consent to having their data submitted to the Canadian and US CF registries and the exceptional effort and contribution from CF clinic team members who collect and enter the data.

Abstract 31:

Evaluation of Metabolic Risk Factors, Physical Activity, and Lifestyle in Lung and Liver Transplant Recipients

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Introduction & Objectives: The trajectory of metabolic risk factors and physical activity (PA) in solid organ transplant recipients have not been well characterized despite their contributions to quality-of-life. We sought to evaluate metabolic risk factors, PA, functional capacity, and lifestyle in lung (LuTR) and liver recipients (LTR) in early and late post-transplant periods.

Methods: 50 LuTR and 50 LTR were recruited from the Ajmera Transplant Centre at the University Health Network between January-March 2020. Metabolic risk factors were abstracted through chart review. An investigator-developed questionnaire was used to survey PA and lifestyle. The Duke Activity Status Index (DASI) was administered to estimate functional capacity. T- and chi-squared tests were used to compare responses between LuTR and LTR, and between those early (<1 year) and late post-transplant.

Results: LuTR were 61 [48-67] years-old, 34% female, and 1.3 [0.8-3.0] years post-transplant, and LTR were 53 [41-60] years-old, 21% female, and 4.0 [1.0 -11.5] years post-transplant. Dyslipidemia was more common in LuTR compared to LTR (58% vs. 18%; P<0.0001), but no difference was observed in hypertension (62% vs. 62%; P>0.99), diabetes (34% vs. 22%; P=0.52), or obesity (26% vs. 26%; P>0.99). 40% LuTR vs. 49% LTR (P=0.29) were participating in ≥150 minutes of moderate-to-vigorous PA weekly, while 85% vs. 73% (P=0.33) reported a desire to increase PA levels. No difference was found in DASI scores (39.5 [19.5-53.7] vs. 48.0 [20.4-58.2]; P=0.16). Metabolic risk factors, PA, and DASI scores did not differ with time post-transplant. Mental health was reported in both early and late post-transplant periods as an important factor in work productivity, sense of accomplishment, and social interactions.

Conclusions: Metabolic risk factors and physical inactivity were common in LuTR and LTR, with no difference between early and late post-transplant periods. Most patients were interested in increasing PA levels and reported mental health as an important factor in daily function.

Support: Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine, Canadian Donation Transplant Research Program, and Pettit Block Grant.

Abstract 32:

Thyrotropin-releasing hormone analog as a stable upper airway-preferring respiratory stimulant with arousal properties

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Introduction & Objectives: Taltirelin is a stable, brain-penetrating thyrotropin-releasing hormone (TRH) analog with minimal endocrine activity and potential respiratory stimulant properties. Taltirelin's receptor target shows high differential expression at the hypoglossal motor nucleus (HMN), and our previous work demonstrated that local TRH microperfusion into the HMN did activate the tongue muscle activities but it is transient, while taltirelin caused the sustained tongue motor activation. To further identify the effects of taltirelin on sleep and breathing, strategy of drug combinations would be taken.

Methods: A randomized, within-subject, repeated measures design over six intervention study days (separated by at least 72 hrs) in chronically instrumented male (n=10) and female (n=9) rats with systemic administration of vehicle controls, taltirelin at two doses, all with or without trazodone (SARIs, can suppress arousal without compromising pharyngeal muscle activity).

Results: Systemically administered taltirelin (1 but not 0.1 mg/kg) increased tonic and within-breath phasic tonic muscle activity compared to vehicle controls ($P < 0.007$), with little or no changes in diaphragm amplitude or respiratory rate. Taltirelin also suppressed non-rapid eye movement (non-REM) sleep and increased trapezius muscle tone in non-REM sleep and decreased total electroencephalogram power and delta (0.5-4 Hz) power ($P < 0.046$).

Conclusion: Taltirelin is a stable upper airway-preferring respiratory stimulant with arousal properties, traits that have potential favorable relevance to some respiratory disorders but not others."

Supported by the Canadian Institutes of Health Research (CIHR).

Abstract 33:

Role of inhibitory brainstem cells in controlling respiratory rhythms

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Introduction: Breathing is an essential and automatic process controlled by connections between brainstem breathing centers to generate respiratory rhythms. The preBötzinger Complex (preBötC) is a key brainstem structure involved in inspiration and contains excitatory and inhibitory cells involved in the coordination of inhalation and exhalation. The role of the excitatory preBötC neurons in inspiration is well studied; however, approximately half of the neurons in the preBötC are inhibitory and how these cells contribute to maintaining respiratory rhythms is unknown.

Objective: We aim to identify the role of the inhibitory preBötC cells in breathing using in vivo optogenetics and hypothesize that optogenetic activation of inhibitory preBötC neurons will depress breathing.

Methods: To study inhibitory neuron activity within the respiratory cycle, we used optogenetics – a technique that uses light to control cell activity – to activate and inhibit the inhibitory preBötC cells while measuring changes in breathing. To measure breathing we recorded diaphragm activity in anesthetized mice, and in freely behaving mice we used whole-body plethysmography.

Results: Activation of inhibitory preBötC cells depresses breathing depending on the point in the respiratory cycle where the laser stimulation occurred by increasing the respiratory period. Photoinhibition of vGAT cells increases the respiratory rate by decreasing the expiratory time and does not change inspiration.

Conclusions: These data suggest that the inhibitory preBötC cells are involved initiating inspiration. Determining the role of inhibitory preBötC cells in coordinating respiratory rhythms will allow us to better understand what is occurring in the brain when breathing is depressed such as in opioid-induced respiratory depression.

Supported by the Ontario Graduate Scholarship (2022-2023), Canadian Institute of Health Research Canadian Graduate Scholarship - Doctoral (2023-2026), CIHR Project Grant and Early Career Investigator Award.

Abstract 34:

Validation of the BACES Mortality Score in Canadian Patients with Nontuberculous Mycobacterial Pulmonary Disease

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1. Department of Medicine, University of Toronto, Toronto. 2. Department of Medicine, University of British Columbia, Vancouver. 3. London Health Sciences Centre, London. 4. Division of Respirology, Toronto Western Hospital, Toronto. "Introduction & Objectives: The clinical course of nontuberculous mycobacterial pulmonary disease (NTM-PD) is variable and difficult to predict. Recently, the BACES score was developed as a tool to predict all-cause mortality in patients with NTM-PD (Kim et al., Am J Respir Crit Care Med 2021;203:230–236). The score is calculated based on five patient characteristics (body mass index, age, cavity, erythrocyte sedimentation rate, and sex), and higher scores portend worse prognosis. Although the BACES score has been validated in South Korean patients, it has not yet been validated in other settings or ethnic groups. The goal of this study is to evaluate the BACES score in a cohort of Canadian patients with NTM-PD.

Methods: We performed a retrospective chart review between July 2003 and June 2021. Patients were eligible for inclusion if they met diagnostic criteria for NTM-PD and excluded if any component of the BACES score was missing. To assess the model's discriminatory performance, we compared Kaplan-Meier curves between risk groups and calculated the Harrell’s C-index. To assess calibration, we used a graphical calibration curve.

Results: The cohort included 435 patients with a median follow up of 5.8 years. The median age was 64 years and 74% were female. Based on their BACES score, patients were classified into three risk groups: low, moderate, and high risk. Survival curves showed clear separation of the risk groups. Harrell’s C-index was 0.733 in our study cohort, indicating good discriminatory performance, although this is lower than the value reported in the derivation cohort (0.812). The graphical calibration curve showed a tendency of the BACES model to underpredict mortality.

Conclusions: The BACES model, originally derived from NTM-PD patients in South Korea, was evaluated in a multicultural cohort of Canadian patients and found to demonstrate good discriminatory performance but suboptimal calibration. Clinicians should be mindful of the limitations of this tool."

Support: MY is supported by the University of British Columbia Clinician Investigator Program.

Abstract 35:

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 (2,6) ,Anna Beale (2,5), Shahidehalsadat Safavi (2,5), Ryan G. L. Koh (8), Dinesh Kumbhare (4,8), Nadia Sharif (2,5), Lianne Singer (2,7), Marc De Perrot (4,6), Laura Donahoe (4,6), John Granton (4,5), Dmitry Rozenberg (2,4,7)

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Rationale: 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 of decreased physiological reserve, may improve prognostication and management 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, 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 of 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 with Fried Frailty Index based on accepted parameters of shrinking, weakness, exhaustion, low activity and slowness. A combination of patient reported outcome measures (Short-form 36, emphasis- 10, New York Heart Association (NYHA) functional class) 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: 60 participants (56±14 years, 73% female, mean BMI 28.1±7.0 kg/m2) completed assessments. 12 (20%) 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 (35±8 vs. 24±10, $p<0.05$) and SF-36 Physical Component Score (23.5 ± 5.2 vs. 34.8±13.3, $p<0.05$). There was no difference observed in SPPB (frail: 8 [6.5-9] vs. non-frail: 9 [8-11], $p=0.1$) or 6-minute walk distance (frail: 423 IQR [376-446] vs. non-frail: 450 [386-525] meters, $p= 0.3$). There were no differences in disease severity measured by mean pulmonary arterial pressure (frail: 38mmHg [30-46] vs. non-frail: 37mmHg [28-45], $p=0.74$) and NYHA functional class III-IV (frail: 4 (57%) vs. non-frail: 15 (58%), $p=1.0$)

Conclusions: Preliminary findings demonstrate that frailty affects over one-fifth of PH patients. Frailty is associated with lower generic and PH specific HRQoL, highlighting that frailty may be able to capture important daily functional limitations outside of PH disease severity. The study is ongoing exploring other frailty constructs and mechanisms of skeletal muscle structure and function.

Funded by Canadian Institute of Health Research-Masters (CIHR-M) and the Sandra Faire and Ivan Fecan Professorship in Rehabilitation Medicine.

Abstract 36:

Reducing metered dose inhaler use in the ambulatory Respirology setting: a quality improvement pilot project

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Introduction & Objectives: Inhalers are commonly used devices to treat obstructive airways disease, with nearly 75% of inhalers prescribed in North America being metered-dose inhalers (MDIs). Environmentally, MDIs are problematic due to the use of hydrofluoroalkane propellants, which are potent greenhouse gases (1,2). Clinically appropriate alternatives to MDIs with a smaller carbon footprint exist, including dry-powder (DPIs) and soft mist inhalers (SMIs). We hypothesized that with education and systems interventions, reducing MDI use is feasible, quantifiable, and could result in meaningful carbon footprint reductions in the ambulatory Respirology setting.

Methods: We implemented a quality improvement project in the outpatient Respirology clinic at Sunnybrook Hospital over a 3-month period. Our objective was to reduce new MDI prescriptions by 30%. Our intervention included physician education, reminders every 4 weeks, posters in clinic areas, and patient handouts focused on the environmental impacts of MDIs. We performed a pre-post analysis of new MDI and non-MDI prescriptions over a 6-month period; 3 months before and after implementing our intervention (completed April 2023). We performed chi-square testing to evaluate for differences in prescriptions before and after the study intervention.

Results: 1353 patient charts were reviewed for new inhaler prescriptions. New MDI prescriptions declined from 27 (24.8%) to 7 (8.2%) during the three months before and after the study intervention, representing a 67% reduction ($p=0.002$). The proportion of monthly MDI/non-MDI prescriptions did not significantly change during the study period, suggesting a durable change in practice pattern. Terbutaline prescriptions increased during the study period (from 1 to 14; $p<0.001$) with no significant differences in overall DPI prescriptions ($p=0.35$). An estimated 550.1kg CO_2 equivalents were saved from reduced MDI prescriptions.

Conclusion: A simple educational and awareness initiative for practitioners and patients can have meaningful impacts on inhaler prescribing patterns and subsequent CO_2 emissions in the ambulatory Respirology setting."

Supported by the Division of Respirology, Department of Medicine, University of Toronto

Abstract 37:

The Comparative Efficacy and Safety of Wakefulness-Promoting Agents for Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnea

Tyler Pitre, MD, MA; Jasmine Mah, MD, MSc; Sarah Roberts, BHSc; Kairavi Desai, BMSc; Yusing Gu, MD; Clodagh Ryan, MD, PhD; Jason W. Busse, DC, PhD; and Dena Zeraatkar, PhD

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Introduction and objective: Excessive daytime sleepiness (EDS) is common among patients with obstructive sleep apnea (OSA). The comparative effectiveness of pharmacological agents is unknown. We sought to compare the effectiveness of drugs for EDS in OSA using network meta-analysis.

Methods: We searched MEDLINE, CENTRAL, EMBASE and clinicaltrials.gov to November 7th, 2022. Reviewers identified randomized trials that enrolled patients with EDS associated OSA on or eligible for conventional therapy assigned to any pharmacological intervention. Paired reviewers independently extracted data addressing effects of drugs on the Epworth Sleepiness Scale (ESS), Maintenance of Wakefulness Test (MWT), and adverse events at the longest reported follow-up. We assessed the certainty of evidence using the GRADE approach.

Results: Fourteen trials (3,085 patients) were eligible. At 4 weeks, compared with placebo, solriamfetol improves ESS scores (mean difference [MD] -3.85 [95% CI -5.24 to -2.50]; high certainty), and armodafinil/modafinil (MD -2.25 [95% CI -2.85 to -1.64]; moderate certainty) and pitolisant/H3 auto-receptor blockers (MD -2.78 [95% CI -4.03 to -1.51]; moderate certainty) probably improves ESS scores. At 4 weeks, compared with placebo, solriamfetol (standardized mean difference [SMD] 0.9 [95% CI 0.64 to 1.17]) and armodafinil/modafinil (SMD 0.41 [95% CI 0.27 to 0.55]) improves MWT (both high certainty), whereas pitolisant/H3 auto-receptor blockers probably do not (moderate certainty). At 4 weeks, Armodafinil/modafinil probably increase the risk of discontinuation due to adverse events (RR 2.01[95% CI 1.14 to 3.51]; moderate certainty); Solriamfetol may increase the risk of discontinuation due to adverse events (RR 2.07 [95% CI 0.67 to 6.25]; low certainty). Low certainty evidence suggests these interventions may not increase the risk of serious adverse events.

Conclusion: Solriamfetol, armodafinil/modafinil and pitolisant reduce daytime sleepiness for patients with OSA already on conventional therapy; with solriamfetol likely superior. Adverse events probably increase the risk of discontinuation of armodafinil/modafinil and may increase the risk of discontinuation with solriamfetol."

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