

**PHYSIOLOGICAL AND CLINICAL RELEVANCE OF IMPAIRED
LUNG DIFFUSING CAPACITY FOR CARBON MONOXIDE
ACROSS THE SPECTRUM OF FIBROSING INTERSTITIAL LUNG
DISEASE SEVERITY: IMPLICATIONS FOR EXERTIONAL
DYSPNEA AND EXERCISE INTOLERANCE**

By

Reginald M. Smyth

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Abstract

Rationale: Patients with fibrosing interstitial lung disease (*f*-ILD) have burdensome exertional dyspnea and exercise tolerance, which are associated with a low lung diffusion capacity for carbon monoxide (DL_{CO}). The precise mechanisms driving “*out-of-proportion*” dyspnea and exercise intolerance in patients with *f*-ILD are poorly understood.

Objectives: To investigate the contribution of a low DL_{CO} to exertional dyspnea and poor exercise tolerance in *f*-ILD patients with 1) largely preserved resting spirometry and 2) a severely reduced (<40% predicted) DL_{CO}.

Methods: All studies included resting pulmonary function tests (PFT) with single-breath DL_{CO} and cardiopulmonary exercise tests (CPET). During CPET, physiological parameters were collected and evaluated, including breathing pattern, operating lung volumes, ventilatory requirements, pulmonary gas exchange, and perceptual responses (Borg 0-10 dyspnea and leg discomfort scores).

General Results: 1) Patients with *f*-ILD and largely preserved resting spirometry had elevated dyspnea and poorer exercise tolerance compared to healthy age- and sex-matched controls and was associated with reduced ventilatory efficiency (i.e., a high ventilation relative to carbon dioxide production, $\uparrow \dot{V}_E/\dot{V}_{CO_2}$). Dyspnea-work rate correlated negatively with DL_{CO} and peak oxygen uptake and positively with $\dot{V}_E/\dot{V}_{CO_2 \text{ nadir}}$. 2) Patients with *f*-ILD and a severely impaired DL_{CO} had elevated dyspnea and poorer exercise tolerance compared to patients with a mild-to-moderately impaired ($\geq 40\%$ predicted) DL_{CO} and healthy controls. These findings were associated with a lower (and flatter) O₂ pulse, an earlier lactate (“anaerobic”) threshold, heightened

submaximal ventilation, lower O₂ saturation, and early critically high inspiratory constraints in the severely impaired DL_{CO} group.

Conclusions: This thesis has enhanced our understanding of DL_{CO} as a physiological biomarker of activity-related impairment across the spectrum of *f*-ILD disease severity. Our data strongly support DL_{CO} as the key index of physiologic impairment from early to end-stage *f*-ILD. Both studies support the current construct that demand-capacity imbalance is paramount to the genesis of exertional dyspnea. Moreover, they also provide a holistic view of the interconnected systemic abnormalities associated with exercise intolerance in *f*-ILD.

Co-authorship

The complete contents of this thesis were prepared by the MSc candidate, Reginald M Smyth, with guidance from supervisors: Dr. J Alberto Neder & Dr. Christopher Parker, lab members: Dr. Matthew James & MSc. Sandra Vincent, and advisory committee members: Dr. Devin Phillips & Dr. Nicolle Domnik (Experimental Medicine Graduate Program, Department of Biomedical and Molecular Sciences, Queen's University). The two manuscripts in this thesis (Chapters 3&4) are the product of research studies designed, curated, analyzed, written, and prepared for publication by the candidate, primary supervisor (Dr. J Alberto Neder), and a group of collaborators.

A version of the manuscript in Chapter 3 has been published in *Respiratory Physiology and Neurobiology* by Smyth et al., 2023 (see "*Study #1 – Authorship Statement:*"). This retrospective study includes data collected between 2010 and 2019 – the candidate was not involved in the primary data collection during this period. However, the candidate performed all data curation for this complete manuscript. The candidate performed all the data analysis for this study, including pulmonary function testing, cardiopulmonary exercise testing (breath-by-breath and 30-second averages), operating lung volumes, and perceptual parameters (Borg 0-10 dyspnea and leg discomfort scores). The candidate performed all statistical analyses and constructed tables and figures for presentation of the study results. Along with the primary supervisor (Dr. J Alberto Neder), the candidate provided the initial interpretation of the results, decided on the study conclusions, and wrote the initial version of the manuscript. All co-authors provided input to the interpretation of the results and conclusions and reviewed and provided feedback on the manuscript. All authors approved the final manuscript included in this thesis.

The manuscript contained in Chapter 4 is a subsequent study building on the findings in *Study #1*. The manuscript has been accepted, peer reviewed, proofed, and is currently awaiting publication in *Respiratory Care* (see “*Study #2 – Authorship Statement:*”). This retrospective study includes data that were collected between 2010 and 2022. The candidate participated in all data collection between 2020 and 2022 as an undergraduate and graduate student but was not involved in data collection before this time. Similarly to *Study #1*, the candidate performed all data analysis including pulmonary function testing, cardiopulmonary exercise testing (breath-by-breath and 30 second averages), operating lung volumes, and perceptual parameters (Borg 0-10 dyspnea and leg discomfort scores). The candidate performed all statistical analyses and constructed tables and figures for presentation of the study results. Along with the primary supervisor (Dr. J Alberto Neder), the candidate provided the initial interpretation of the results, decided on the study conclusions, and wrote the initial version of the manuscript. All co-authors provided input to the interpretation of the results and conclusions and provided feedback on the manuscript. All authors approved the final manuscript included in this thesis.

Study #1 - Authorship Statement:

Reginald M Smyth (BSc)¹: Conceptualization, Data curation, Formal analysis, Writing - original draft; **J Alberto Neder (MD)**¹: Conceptualization, Data curation, Formal analysis, Funding acquisition, Supervision, Writing - original draft; **Matthew D James (PhD)**¹: Data curation, Writing: review & editing; **Sandra G Vincent (MSc)**¹: Data curation, Project administration; **Kathryn M Milne (MD)**^{1,2}: Data curation, Writing: review & editing; **Mathieu Marillier (PhD)**³: Data curation, Writing: review & editing; **Juan P de-Torres (MD)**¹: Writing - review & editing; **Onofre Moran-Mendoza (MD)**¹: Conceptualization, Data curation, Supervision, Writing - review & editing; **Denis E O'Donnell (MD)**¹: Conceptualization, Funding acquisition, Supervision, Writing - review & editing; **Devin B Phillips (MD)**¹: Conceptualization, Data curation, Formal analysis, Supervision, Writing - original draft.

1. Department of Medicine, Queen's University and Kingston Health Sciences Centre Kingston General Hospital, Kingston, ON, Canada.
2. Centre for Heart Lung Innovation, Providence Health Care Research Institute, University of British Columbia, St. Paul's Hospital, Vancouver, BC, Canada.
3. HP2 Laboratory, INSERM U1300, Grenoble Alpes University, Grenoble, France.

Study #2 - Authorship Statement:

Reginald M. Smyth (BSc)^{1,2}: Literature search, Data collection, Analysis of data, Manuscript preparation, Review of the manuscript; **Dr. Matthew D. James (PhD)¹:** Data collection, Analysis of data, Review of the manuscript, **Sandra G. Vincent (MSc)¹:** Data collection, Analysis of data, Review of the manuscript; **Dr. Kathryn M. Milne (MD)^{1,3}:** Data collection, Analysis of data, Review of the manuscript; **Dr. Mathieu Marillier (PhD)⁴:** Data collection, Analysis of data, Review of the manuscript; **Dr. Nicole J. Domnik (PhD)^{1,2}:** Data collection, Analysis of data, Review of the manuscript; **Dr. Christopher M. Parker (MD)¹:** Study design, Analysis of data, Review of the manuscript; **Dr. Juan P. de-Torres (MD)^{1,5}:** Data collection, Analysis of data, Review of the manuscript; **Dr. Onofre Moran-Mendoza (MD)¹:** Study design, Data collection, Analysis of data, Manuscript preparation, Review of the manuscript; **Dr. Devin B. Phillips (PhD)^{1,6}:** Study design, Data collection, Analysis of data, Review of the manuscript; **Dr. Denis E. O'Donnell (MD)¹:** Study design, Analysis of data, Review of the manuscript; **Dr. J. Alberto Nader (MD)¹:** Study design, Analysis of data, Manuscript preparation, Review of the manuscript.

1. Respiratory Investigation Unit, Division of Respirology, Department of Medicine, Queen's University and Kingston Health Sciences Centre, Kingston General Hospital, Kingston, ON, Canada.
2. Department of Biomedical and Molecular Sciences and Department of Medicine, Queen's University, Kingston, ON, Canada.
3. Centre for Heart Lung Innovation, Providence Health Care Research Institute, University of British Columbia, St. Paul's Hospital, Vancouver, BC, Canada.
4. HP2 Laboratory, INSERM U1300, Grenoble Alpes University, Grenoble, France.
5. Pulmonary Department, Clínica Universidad de Navarra and Instituto de Investigación Sanitaria de Navarra (IdiSNA), Navarra, Spain.
6. School of Kinesiology and Health Science, Faculty of Health, York University, Toronto, ON, Canada.

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List of Abbreviations

Abbreviation	Meaning
ANOVA	Analysis of variance
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CPFE	Combined Pulmonary Fibrosis and Emphysema
CT	Computed tomography
DL _{CO}	Diffusion capacity of the lung for carbon monoxide
EILV	End-inspiratory lung volume
f_B	Breathing frequency
FEV ₁	Forced expiratory volume in one second
f_{ILD}	Fibrosing interstitial lung disease
FRC	Functional residual capacity
FVC	Forced vital capacity
IC	Inspiratory capacity
ILD	Interstitial lung disease
IND	Inspiratory neural drive
iNO	Inhaled nitric oxide
IPF	Idiopathic pulmonary fibrosis
IRV	Inspiratory reserve volume
K _{CO}	Transfer coefficient for carbon monoxide (DL _{CO} /V _A)
KHSC	Kingston Health Science Centre
LLN	Lower limit of normal
LTOT	Long term oxygen therapy
mMRC	Modified Medical Research Council (0-4)
MVV	Maximal voluntary ventilation
PaCO ₂	Arterial partial pressure for carbon dioxide
PaO ₂	Arterial partial pressure for oxygen
PAP	Pulmonary arterial pressure

P_{ETCO_2}	End-tidal partial pressure of carbon dioxide
PFT	Pulmonary function test
RER	Respiratory exchange ratio
SD	Standard deviation
S_{pO_2}	Oxygen saturation by pulse oximetry
T_E	Expiratory time
T_I	Inspiratory time
TLC	Total lung capacity
T_{TOT}	Total respiratory time
V_A	Alveolar volume
\dot{V}_A/\dot{Q}_c	Alveolar ventilation-capillary perfusion relationship
VC	Vital capacity
\dot{V}_{CO_2}	Carbon dioxide output
V_D	Dead space
\dot{V}_E	Expired minute ventilation
\dot{V}_E/\dot{V}_{CO_2}	Ventilatory equivalent for carbon dioxide
\dot{V}_{O_2}	Oxygen uptake
VR_{dyn}	Dynamic ventilatory reserve
V_T	Tidal volume

Chapter 1:

General Introduction

1.1 General Introduction

Interstitial lung disease (ILD) is an umbrella term encompassing several heterogeneous lung diseases characterized by varied degrees of inflammation, fibrosis, and scarring of the pulmonary parenchyma (Wijsenbeek et al., 2022). Fibrosing ILD (*f*-ILD) is a specific phenotypical expression of ILD characterized by a particularly high risk of progressing fibrosis (Cottin et al., 2019). *f*-ILD progression is reflected by an increase in fibrotic features on computed tomography (CT) scans, a decrease in dynamic (maneuvers dependent on the amount of time taken for the exhalation process) and “static” (measurements of absolute lung volumes that are not affected by the rate of air movement but still require some air movement and therefore are not truly “static” measurements) lung volumes, and a worsening of gas exchange (reflected in a low diffusion capacity of the lung for carbon monoxide (DL_{CO}) and/or arterial partial pressure for oxygen (PaO₂)) (Cottin et al., 2019). In varying degrees, these factors contribute to increased disability, reduced health-related quality of life, and early mortality in those with idiopathic pulmonary fibrosis (IPF), the prototypical *f*-ILD (Cottin et al., 2019). In 2011, for all ages, the broad prevalence and incidence of IPF were 45.4 per 100,000 (7688 cases) and 21.3 per 100,000 (1784 cases) for Canadian men, respectively, and 38.2 per 100,000 (3047 cases), and 16.2 per 100,000 (1273 cases) for Canadian women respectively (Hopkins et al., 2016). Further, the four-year risk of death for Canadian IPF patients was 41%, and the quality of life with IPF after two years was lower than for chronic obstructive pulmonary disease stage IV defined by the Global Initiative for Chronic Lung Disease (Hopkins et al., 2016; Ståhl et al., 2005).

Shortness of breath (commonly termed breathlessness or dyspnea) is one of the most common and disabling symptoms reported by patients with IPF (Bonini & Fiorenzano, 2017) and other *f*-ILDs (Dias et al., 2018; Kallianos et al., 2015). The American Thoracic Society defines dyspnea as “*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*” (Parshall et al., 2012). The perceived intensity of dyspnea is especially burdensome during physical activity and often encourages exercise avoidance, perpetuating a vicious cycle of respiratory and peripheral muscular deconditioning and further breathlessness (Bonini & Fiorenzano, 2017). Despite the advent of pharmacological strategies (i.e., antifibrotics) aimed at slowing disease progression, *f*-ILD is often not diagnosed early enough to optimize the slowing of pulmonary fibrosis (McCarthy & Keane, 2022). Furthermore, a lack of effective treatment options for patients with *f*-ILD in its advanced stages sequesters patients to a life of worsening dyspnea (Wijsenbeek et al., 2019). Improving our understanding of the physiological underpinnings of dyspnea and exercise intolerance in *f*-ILD and establishing metrics for gauging fibrosis progression in its early stages have, therefore, become more of a clinical priority in the past decade (McLean et al., 2021; Molina-Molina et al., 2018).

There are a plethora of physiologic studies on the genesis of exertional dyspnea in ILD (Dias et al., 2018; Faisal et al., 2016; Jensen et al., 2018; Milne et al., 2020b; O'Donnell et al., 1998) and other prevalent respiratory diseases (Milne et al., 2023; Moore et al., 2018; O'Donnell et al., 2019a) indicating that the symptom primarily reflects a growing mismatch between the demand to breathe and the capacity of the respiratory system to meet such heightened requirements (Faisal et al., 2016; O'Donnell et al., 1998). The restrictive nature of *f*-ILDs, characterized by decreasing lung compliance and increasing work of breathing, has been emphasized as the primary factor contributing to this demand-capacity imbalance and thus, dyspnea intensity and exercise

intolerance (Faisal et al., 2016; O'Donnell et al., 1998). However, this tends to overshadow the important contributory role of inefficient gas exchange to symptom intensity, namely increased wasted ventilation in the dead space (V_D) (Robertson, 2015). In fact, most clinicians assume that it is unlikely that patients with no or only mild restriction would present with ventilatory and/or gas exchange abnormalities severe enough to elicit exertional dyspnea (Oldham et al., 2022). This is despite approximately a third of patients seeking care at Kingston Health Science Center (KHSC) having no or mild restriction on pulmonary function testing (PFT) but still report high daily breathlessness (personal communication from Dr. J Alberto Neder, according to the KHSC PFT database).

It should also be recognized that dyspnea is not the sole complaint of physically limited *f*-ILD patients, as the perceived feeling of fatigue and leg discomfort are reported by a significant fraction of patients with more advanced disease (Marillier et al., 2021b; Schaeffer et al., 2017). In close similarity with other chronic pulmonary diseases (Basso et al., 2013; Santos et al., 2019), therefore, the cardiocirculatory-skeletal muscle axis might bear a more prominent contributory role to early exercise termination in patients at the later stages of the disease (Holland, 2010; Miller et al., 1995). Indeed, the burden of exertional symptoms as the disease progresses – both “central” (dyspnea) and “peripheral” (leg discomfort) – varies markedly amongst patients with apparently similar levels of ventilatory impairment (Molgat-Seon et al., 2020; Schaeffer et al., 2017). Thus, it is conceivable that the relevance of non-respiratory (i.e., cardiovascular/muscular) factors leading to poor exercise tolerance increases in *f*-ILD patients at the later stages of their disease.

Based on these premises, **the overarching goal of this thesis was to examine the relationships between lung mechanical and gas exchange abnormalities, cardio-muscular derangements (heart rate, O₂ pulse, and anaerobic threshold), exertional symptoms, and**

exercise intolerance in *f*-ILD patients across the spectrum of disease severity. Specifically, the following research questions drove *Study #1* (Chapter 3): 1) do *f*-ILD patients with normal spirometry and only mild restriction on body plethysmography have increased dyspnea (at rest and during exercise) and lower exercise tolerance compared to healthy age- and sex-matched controls; and 2) if so, what are the key mechanisms underlying these abnormalities in this specific sub-population? The answers to this initial question led to a subsequent study aimed at uncovering the systemic mechanisms driving poor exercise tolerance in *f*-ILD patients with advanced disease as signaled by a severely impaired DL_{CO} (<40% predicted) (*Study #2*, Chapter 4).

Chapter 2:

Literature Review

2.1 Fibrosing Interstitial Lung Disease and Dyspnea

ILD is an umbrella term for over 200 heterogeneous lung diseases characterized by inflammation, fibrosis, and scarring, resulting in poor lung compliance and low dynamic and “static” lung volumes (Wijsenbeek et al., 2022). ILDs include several diseases of unknown causes and others that are related to environmental exposures or occur secondary to specific diseases, such as connective tissue diseases (Wijsenbeek et al., 2022). Due to the large number of ILDs, their heterogeneous presentation, and usually unknown etiology, it has been proposed that for clinical research and, potentially, for treatment, ILDs with similar biological and clinical behaviours be categorized together (Flaherty et al., 2017).

f-ILD describes any ILD with diffuse pulmonary parenchymal disease (usually idiopathic) with tomographic features of fibrosis in a patient at risk of developing further fibrosis (Cottin et al., 2019). The progression of *f*-ILD is reflected in an increase in fibrotic features on CT, restriction of lung volumes, and worsening of gas exchange (Cottin et al., 2019). *f*-ILDs are particularly interesting as they share common pathogenic mechanisms with IPF, one of the most common subtypes (Raghu et al., 2011). Patients with other specific ILDs are also at risk of developing a progressive fibrotic phenotype (Cottin et al., 2019), including idiopathic nonspecific interstitial pneumonia (Belloli et al., 2016), unclassifiable idiopathic interstitial pneumonia (Hyldgaard et al., 2017), autoimmune ILDs (Fischer & Chartrand, 2015), chronic sarcoidosis (Patterson & Streck, 2013), chronic hypersensitivity pneumonitis (Fernández Pérez et al., 2013), and exposure-related ILDs such as ILD developed from asbestos inhalation (Khalil et al., 2007) (Figure 1).

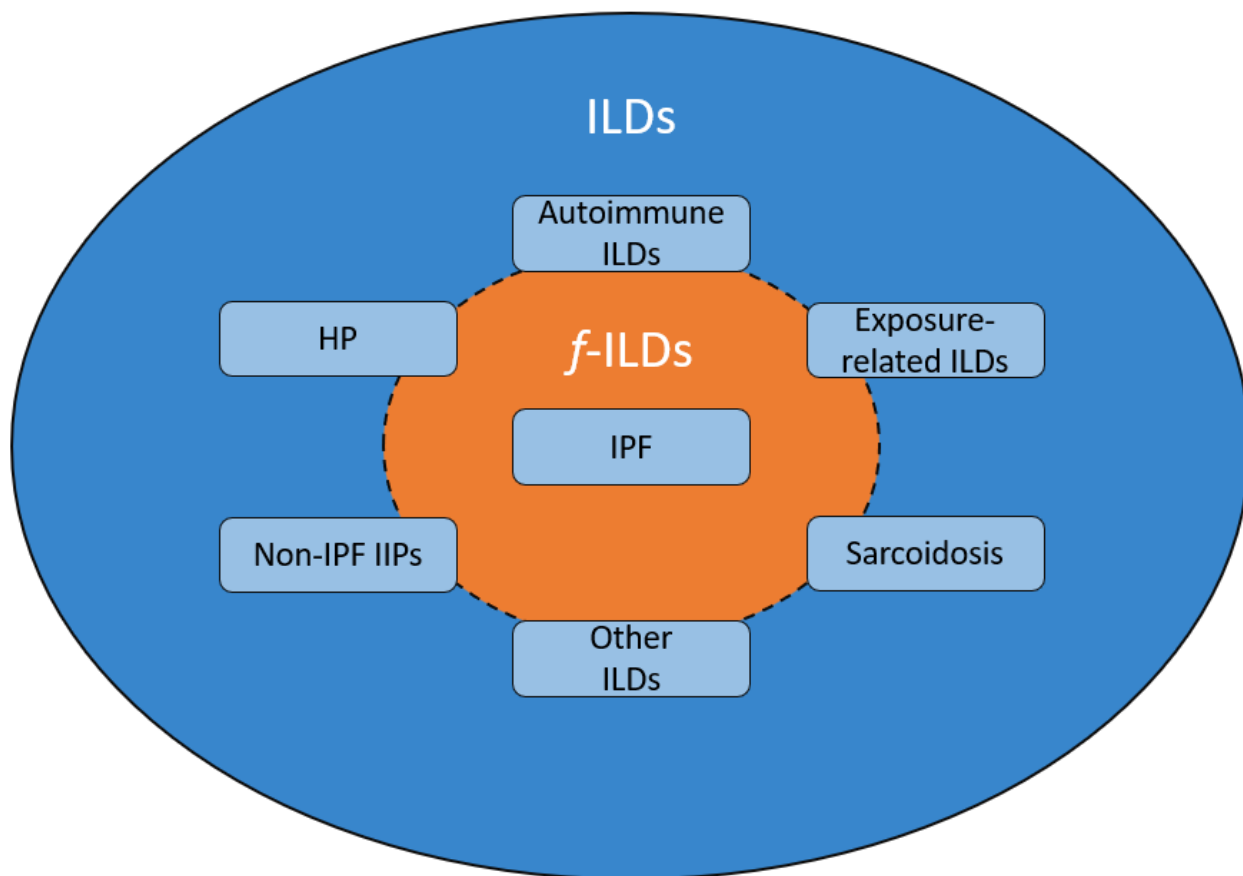


Figure 1. Types of interstitial lung diseases (ILDs) at risk of developing a progressive fibrosing phenotype consistent with the definition of fibrosing ILD (*f*-ILD). (*Chapter 2*)
Definition of abbreviations: HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; IIPs: idiopathic interstitial pneumonias (Figure adapted from (Cottin et al., 2019)).

Dyspnea is one of the most common and disabling symptoms reported by patients with IPF (Bonini & Fiorenzano, 2017), the prototypical *f*-ILD (Cottin et al., 2019; Oldham et al., 2022). Perceived dyspnea intensity can become particularly burdensome during physical activity, often leading to exercise avoidance and a deleterious cycle of progressive respiratory and muscular deconditioning and further breathlessness. (Bonini & Fiorenzano, 2017). This disabling symptom also contributes to worsening health-related quality of life, exercise intolerance, and increased mortality in as many as 41.8 per 100,000 Canadian men and women with IPF in 2011 (Hopkins et al., 2016), justifying a need for a better understanding of the mechanisms underlying dyspnea in *f*-ILD.

2.2 Utility of DL_{CO} and CPET for Understanding Dyspnea and Exercise Intolerance

Activity-related dyspnea in *f*-ILD is a sensation influenced by various concomitant mechanical and chemical stimuli from the respiratory, cardiovascular, and muscular systems (Neder, 2023). Given the integrative nature of *f*-ILD pathology, it is not surprising that resting spirometry is insufficient to explain the underlying mechanisms of activity-related dyspnea as it only accounts for resting lung mechanics and not the cardiovascular and muscular inputs to the genesis of activity-related dyspnea (Neder, 2023). The heterogeneity of *f*-ILDs presents challenges for clinicians and patients in implementing effective treatment options, often requiring more comprehensive testing than spirometry alone to understand the underlying causes of dyspnea (AmericanThoracicSociety, 2000).

DL_{CO} is a common PFT that can provide helpful information about the underlying mechanisms of dyspnea and exercise intolerance in patients with cardiopulmonary diseases. The DL_{CO} is an indicator of the lung's ability to transfer gases from the external environment to the bloodstream (Hughes, 2003). DL_{CO} has also been used to predict exercise-induced oxygen desaturation in ILD patients (Agustí et al., 1991; Risk et al., 1984). The single-breath method involves the inhalation of a gaseous mixture containing carbon monoxide (CO) (0.3%), tracer gas (usually methane, 0.3%), O₂ (21%), and balance nitrogen. CO has a high affinity for hemoglobin (200 to 250 times that of O₂) and readily diffuses across the alveolar-capillary membrane. Conversely, the tracer gas is a relatively large molecule and does not diffuse well. Upon exhalation, in a healthy lung, most of the carbon monoxide diffuses into the bloodstream and returns a minimal concentration to the external environment. Conversely, A larger magnitude of tracer gas will be returned to the external environment compared to carbon monoxide, albeit still diluted compared to the initial inhaled tracer gas concentration when accounting for the residue air left in the lung

after complete exhalation (i.e., Residual volume). These concentrations are then analyzed by sensors at the mouthpiece and compared to each other to determine the DL_{CO} . It has been consistently shown that, with the progression of ILD severity, the DL_{CO} also becomes worse, reflecting a worsening of gas exchange efficiency (Agustí et al., 1991; Bonini & Fiorenzano, 2017; Dias et al., 2018; Wagner et al., 1976; Wémeau-Stervinou et al., 2012).

DL_{CO} , like any clinical test, has limitations and must be interpreted carefully. One of the most important considerations is the effect of lung volume on the DL_{CO} (Kaminsky et al., 2007; Stam et al., 1991). Individuals with larger lung volumes tend to have more functional alveolar units and, therefore, a more substantial ability to distribute ventilation across a larger surface area, allowing for more efficient gas exchange. Thus, even if gas exchange is inefficient at the level of a single alveolus, larger lung volumes can confer a “*protective effect*” against pathologies that might hinder gas exchange while still producing relatively preserved DL_{CO} measurements. As such, the DL_{CO} is usually reported as an absolute value as well as an absolute value normalized for alveolar volume (V_A) (DL_{CO}/V_A), known as the transfer coefficient (K_{CO}).

Another essential tool for understanding the mechanisms underlying dyspnea and exercise intolerance is incremental cardiopulmonary exercise testing (CPET). CPET is considered the gold standard for assessing symptom-limited exercise intolerance (Palange et al., 2007) and can provide a comprehensive assessment of the physiologic changes that occur in the respiratory, cardiovascular, and musculoskeletal systems (Sue & Wasserman, 1991) during progressive exercise. Compared to rest, CPET exaggerates many key physiologic processes that would contribute to dyspnea and exercise intolerance, including excessive expired minute ventilation (\dot{V}_E), cardiocirculatory impairment, exercise-induced hypoxemia, breathing pattern and lung mechanical abnormalities, and peripheral muscle fatigue (Stickland et al., 2022). There is no clear

consensus on whether CPET performed on a cycle ergometer or treadmill is better suited for evaluating people with *f*-ILD. The cycle ergometer provides a more controlled and quantifiable increase in work rate; however, the treadmill better simulates daily activities (Wasserman et al., 1994). That said, cycle ergometer-based CEPT is likely the better option for understanding the mechanisms underlying dyspnea in *f*-ILD as less muscle mass activation (i.e., less O₂ extraction and, consequently, greater mixed venous O₂ content) and an earlier anaerobic threshold (i.e., higher ventilation at lower exercise intensities) mitigate the severity of exercise-induced hypoxemia compared to walking (Neder, 2023)

Collectively, the data derived from spirometry, lung volume measurements, DL_{CO} and CPET can jointly provide a multifactorial assessment of the integrative physiology contributing to exercise intolerance when compared to normative data accounting for age and sex (Hall et al., 2021; Neder et al., 2020; Quanjer et al., 2012; Stanojevic et al., 2017).

2.3 Pulmonary Gas Exchange Inefficiency and Dyspnea in *f*-ILD

The most fundamental role of the respiratory system is to facilitate sufficient gas exchange between the circulatory system and the external environment in response to peripheral O₂ needs while removing metabolically produced CO₂ (Dempsey & Smith, 2014; Glenny & Robertson, 2011). Arterial blood gas homeostasis is ensured through the appropriate matching of alveolar ventilation (\dot{V}_A) and capillary perfusion (\dot{Q}_c) to minimize: 1) distribution of air to poorly perfused alveolar units, reducing dead space ventilation, which is the volume of ventilated air not participating in gas exchange; and 2) distribution of blood flow to poorly ventilated alveolar units, reducing venous admixture (volume of deoxygenated blood from the venous circulation that did not participate in gas exchange, seemingly “bypassing” the lungs) (J. A. Neder et al., 2022a).

Optimization of \dot{V}_A/\dot{Q}_c matching during exercise reduces respiratory discomfort and allows for sustained dynamic exercise with increased physiological demand.

As mentioned, *f*-ILDs involve pathologic abnormalities affecting multiple lung areas, including the airways, alveolar tissue, and lung parenchyma (Cottin et al., 2018). Depending on the relative contribution of these abnormalities, \dot{V}_A/\dot{Q}_c matching can be differentially affected. For example, airway and alveoli dominant fibrosis tends to restrict lung volumes and lead to low \dot{V}_A relative to \dot{Q}_c . The consequences of $\downarrow \dot{V}_A/\dot{Q}_c$ matching are: 1) CO_2 retention (increased arterial partial pressure of CO_2 ($\uparrow P_a\text{CO}_2$)); 2) a greater magnitude decrease in $P_a\text{O}_2$ ($\downarrow\downarrow P_a\text{O}_2$) relative to the magnitude of $P_a\text{CO}_2$ increase ($\uparrow P_a\text{CO}_2$); and 3) increased pulmonary arterial pressure (PAP) secondary to hypoxic pulmonary vasoconstriction (J. A. Neder et al., 2022a; Sarkar et al., 2017). Through various mechanisms, these factors increase afferent stimuli to the brain to increase inspiratory neural drive (IND) and subsequently \dot{V}_E (Faisal et al., 2016; Milne et al., 2020b). Conversely, parenchyma-dominant disease can cause damage and morphometric change to the pulmonary capillaries, resulting in high \dot{V}_A relative to \dot{Q}_c (J. A. Neder et al., 2022a; Sarkar et al., 2017). The consequences of $\uparrow \dot{V}_A/\dot{Q}_c$ matching is high V_D relative to tidal volume (V_T , V_D/V_T) leading to increased \dot{V}_E secondary to heightened IND (Faisal et al., 2016; Milne et al., 2020b). In late disease, high and low \dot{V}_A/\dot{Q}_c matching is present throughout the lung and would be reflected by a low DL_{CO} (Agustí et al., 1991). It is important to note, however, that the DL_{CO} is sensitive to but not specific for \dot{V}_A/\dot{Q}_c mismatching, e.g., alveolar-capillary diffusion limitation might cause a low DL_{CO} irrespective of the degree of \dot{V}_A/\dot{Q}_c mismatching (Agustí et al., 1991; Bonini & Fiorenzano, 2017; Wagner et al., 1976). Regardless, the presence of \dot{V}_A/\dot{Q}_c mismatching will drive increases in \dot{V}_E relative to carbon dioxide output (\dot{V}_{CO_2}) ($\uparrow \dot{V}_E/\dot{V}_{\text{CO}_2}$, termed ventilatory equivalent

for carbon dioxide) secondary to heightened IND to maintain arterial blood gas homeostasis (Gale et al., 1985) contributing to worsening dyspnea and exercise tolerance (J. A. Neder et al., 2022a).

Although the exact mechanistic relationship between increased \dot{V}_E and dyspnea in *f*-ILD remains poorly understood, it has been well documented that patients with moderate to severe ILD have elevated dyspnea at any given \dot{V}_E during exercise compared to healthy age-matched controls (Faisal et al., 2016; Milne et al., 2020b; O'Donnell et al., 1998). Various afferent stimuli from the respiratory, cardiovascular, and muscular systems continuously report to the central controller; thus, elevated ventilation and, subsequently, dyspnea, are usually the product of multiple concomitant inputs (Dempsey & Smith, 2014; Neder, 2023). Therefore, factors that would contribute to elevated \dot{V}_E , including pulmonary restriction/reduced compliance, gas exchange impairment, and muscular dysfunction/deconditioning (topics to be further discussed below), would be expected to contribute to heightened dyspnea intensity and exercise intolerance.

2.4 Lung Mechanics and the Ventilatory Response to Exercise in *f*-ILD

In health, exercise-induced increases in \dot{V}_E are primarily achieved by an increase in V_T until it reaches ~50-60% of the vital capacity (VC) (Molgat-Seon et al., 2020). Further stimulation to increase \dot{V}_E as work rate also increases results in a more dominant increase in breathing frequency (f_B) rather than V_T , reflecting a steepening of the \dot{V}_E - V_T relationship. (Molgat-Seon et al., 2020; Sietsema et al., 2020). This breathing pattern is considered optimal as it minimizes the elastic loading of the respiratory system by allowing V_T expansion to occur in the linear portion of the pressure-volume relationship (Axe & Abbrecht, 1985) and minimizes the fraction of V_T “wasted” in the V_D (Johnson et al., 1994). In moderate to advanced *f*-ILD, however, inflammation, scarring, and fibrosis of the pulmonary parenchyma leads to a reduction in lung compliance and a characteristic restrictive pattern in lung function, namely, a decrease in lung volumes (total lung

capacity (TLC) and VC) compared to healthy individuals (Faisal et al., 2016; Milne et al., 2020b). This contributes to 1) limited V_T expansion and, therefore, reduced maximal voluntary ventilation (MVV) and 2) increased mechanical and metabolic cost of breathing for a given \dot{V}_E . Reduced VC, MVV, and lung compliance alter the ventilatory response to exercise.

At rest, *f*-ILD patients typically have a rapid breathing pattern (i.e., normal-low V_T but high f_B). During incremental exercise, patients with *f*-ILD will initially increase \dot{V}_E by increasing V_T like healthy individuals. However, V_T will plateau at a much lower \dot{V}_E and exercise intensity due to the reduced VC. Many studies in ILD have reported an upward inflection in dyspnea intensity as V_T expansion approaches VC (Faisal et al., 2016; Milne et al., 2020b; O'Donnell et al., 1998). This inflection is thought to be the result of mismatching in efferent motor signals to the respiratory muscles and afferent mechanoreceptor signals generated by stretching of lung tissue and the respiratory muscles (Manning & Schwartzstein, 1995) (i.e., increased respiratory muscle activation with diminished returns in further increases to V_T), although this has yet to be directly tested. Using an esophageal catheter with multi-paired electrodes, Faisal et al. (2016) and Milne et al. (2020b) indirectly measured the electrical activation of the diaphragm during exercise and found that tidal activation of the diaphragm inflects upwards commensurate with dyspnea intensity at the point of V_T plateauing (indicating inspiratory constraint). Once V_T reaches ~60% of the VC, subsequent increases in \dot{V}_E are then achieved by further increasing f_B (usually occurring much sooner during exercise compared to healthy individuals) (Faisal et al., 2016; Milne et al., 2020b; Molgat-Seon et al., 2020). This rapid and shallow breathing pattern means that the V_D/V_T is typically higher during exercise in patients with *f*-ILD vs. health; thus, a larger proportion of V_T is not participating in gas exchange, an abnormality likely reflected by a low DL_{CO} .

2.5 Additional Underpinnings of Pulmonary Gas Exchange Impairment in *f*-ILD

The characteristic inflammatory and fibrotic progression of *f*-ILDs may result in significant alterations of the pulmonary parenchyma, cardiovascular system, and lung vasculature, which would change the distribution of pulmonary blood flow, contributing to \dot{V}_A/\dot{Q}_c mismatching and gas exchange inefficiency.

2.5.1 Diffusion Limitation

Diffusion capacity describes the ability of gases to migrate between the alveoli and pulmonary capillaries and is almost always impaired in ILD patients, contributing to a low DL_{CO} and K_{CO} (Faisal et al., 2016). As described by Fick's Law of diffusion, the diffusion capacity of gases depends upon the shared surface area of the alveolar-capillary membrane and the parenchymal thickness separating the capillary and alveoli, among other variables (Equation 1).

(Equation 1)
$$\dot{V}_{\text{gas}} \propto \frac{A}{T} \cdot D \cdot (P_1 - P_2)$$

\dot{V}_{gas} : rate of gas transfer across the pulmonary parenchyma

A: surface area available for gas exchange

T: parenchymal thickness

$(P_1 - P_2)$: partial pressure gradient

D: diffusion coefficient $\left(\frac{\text{Solubility}}{\sqrt{\text{molecular weight}}} \right)$

In patients with ILD, impaired gas diffusion between the alveoli and associated pulmonary capillaries results from a thickening of the alveolar-capillary membrane and a reduction in pulmonary capillary blood volume (Roughton & Forster, 1957). Previous biopsies of human lungs with diffuse IPF indicate that the alveolar-capillary membrane is approximately two-fold thicker versus healthy individuals (Cassan et al., 1974). ILD patients also exhibit reduced pulmonary capillary blood volume, presumably due to the capillaries' destruction, obstruction, and/or compression in areas of increased fibrosis (Renzoni et al., 2003). Accordingly, impaired

pulmonary diffusion and reduced capillary blood volume have been demonstrated in ILD and seem to both contribute to a reduced DL_{CO} (Wémeau-Stervinou et al., 2012).

A critical characteristic of diffusion limitation is the development or worsening of hypoxemia during exercise (Faisal et al., 2016; Sarkar et al., 2017). Theoretically, diffusion limitation should cause both hypoxemia and hypercapnia; however, hypercapnia is uncommon due to diffusion limitation since CO_2 is 20 times more soluble in water than O_2 (Sarkar et al., 2017; West, 1971), and most patients with ILD can increase \dot{V}_E to wash out CO_2 (West, 1971). Thus, ILD patients usually have normal or mildly reduced P_aCO_2 and only retain CO_2 during the late stages of the disease (Risk et al., 1984). During exercise, the combination of increased parenchymal thickness and reduced pulmonary capillary volume means that alveoli in areas of increased fibrosis are unlikely to sufficiently saturate the capillary blood with O_2 , resulting in a widening of the alveolar-arterial oxygen gradient and a subsequent fall in mixed venous oxygen levels (Sarkar et al., 2017). It should be noted, however, that studies using multiple inert gas elimination techniques suggest that resting hypoxemia in ILD is mainly explained by \dot{V}_A/\dot{Q}_c mismatching and not parenchymal thickening (Agustí et al., 1991; Wagner et al., 1976) however, parenchymal thickening likely still contributes to reduced capillary blood volume and reduced V_A with disease progression. Regardless, the development of hypoxemia has implications for both increased dyspnea intensity, through hypoxic chemical stimulation of the peripheral chemoreceptors to increase ventilation, and exercise limitation, through reduced O_2 delivery to the peripheral muscles inducing an earlier shift to anaerobic metabolism (Marillier et al., 2023a; Marillier et al., 2021b).

2.5.2 Central Hemodynamics

f-ILD pathologies often involve the obliteration of the pulmonary capillary bed (Nathan et al., 2007). Further, in advanced *f*-ILD, it is common for patients to exhibit hypoxemia at rest, leading to hypoxic pulmonary vasoconstriction, an attempt of the pulmonary vasculature to divert blood away from poorly ventilated alveoli (Zangiabadi et al., 2014). During exercise, hypoxemia may be further worsened by reduced blood cell transit time in vasoconstricted capillaries; however, this is speculative (Sun et al., 2001). Both obliteration of the capillary bed and vascular remodeling contribute to increased pulmonary vascular resistance and an associated increase in PAP, a common comorbidity of *f*-ILD patients (Nathan et al., 2007). Capillary/pre-capillary hypertension has direct implications for cardiac function. Transmission of the elevated PAP increases right ventricular pressure. To maintain cardiac output, the right ventricle must perform more work to overcome the elevated PAP, significantly stressing the right ventricular wall (Bogaard et al., 2009). Over time, ILD patients may develop right ventricular hypertrophy and, ultimately, right ventricular failure (Kolb & Hassoun, 2012). As right ventricular function declines, stroke volume is reduced, and contractile time increases, leading to contractile asynchrony between the left and right ventricles and impaired left ventricular filling (Vonk Noordegraaf & Galiè, 2011).

2.6 Skeletal Muscle Dysfunction

Respiratory and skeletal muscle deconditioning are frequently observed in patients with ILD and tend to promote dyspnea and exercise intolerance (Panagiotou et al., 2016). “Skeletal muscle dysfunction” typically refers to physiologic changes to the skeletal muscle that hinder muscular function (i.e., reduced muscle strength, endurance, and/or resistance to fatigue) (Mador & Bozkanat, 2001; Molgat-Seon et al., 2019). The structure and function of the respiratory muscles are also thought to be affected in patients with ILD (Panagiotou et al., 2016). While the exact

mechanisms of skeletal muscle dysfunction in ILD are not well understood, various factors are known to contribute to skeletal muscle dysfunction, namely, inflammation, oxidative stress, malnutrition, hypoxemia, and deconditioning (Panagiotou et al., 2016). It seems likely that the latter two play critical roles in muscle dysfunction.

There is increasing evidence that hypoxemia in ILD might be related to muscular dysfunction (Holland, 2010). Low O₂ delivery due to hypoxemia may cause muscle hypoxia, thus increasing anaerobic metabolism. Notably, previous work by Marillier and colleagues demonstrated that hypoxemia does affect the skeletal muscles, as alleviation of hypoxemia via supplemental O₂ decreased leg fatigue by one Borg unit in 15 *f*-ILD patients with severe exertional hypoxemia during exercise (Marillier et al., 2021b).

As mentioned, the experience of activity-related dyspnea can be enough to dissuade ILD patients from performing physical activity. In this case, muscular deconditioning and atrophy can occur. Previous work in chronic obstructive pulmonary disease has found negative associations regarding physical inactivity and exercise capacity and positive associations with type 1 muscle fiber reduction, percentage of intramuscular fat, and quadriceps attenuation (Maddocks et al., 2014). The link between inactivity and reductions in type 1 muscle fibers likely reflects a reduced capacity for oxygen uptake and, subsequently, earlier fatigue. The implications of this, during exercise, are that the anaerobic threshold occurs earlier and at lower work rates in a patient with ILD compared to a healthy individual and has adverse consequences, including reduced energy production, excess CO₂ production, and loss of acid-base homeostasis (Mador & Bozkanat, 2001). The latter two can become exaggerated by the premature production of lactic acid that may increase dyspnea (higher ventilatory demand) and leg discomfort, ultimately contributing to exercise intolerance.

2.7 Summary and Objectives & Hypothesis

2.7.1 Summary

There are clear associations between restrictive respiratory mechanics, impaired gas exchange efficiency, and heightened dyspnea intensity in patients with moderate to severe *f*-ILD, all contributing to early exercise cessation. To date, however, no study has explored the underlying mechanisms of dyspnea in patients at the extremes of *f*-ILD severity: those with mild disease and largely preserved resting spirometry (*Study #1*), or the physiological mechanisms driving poor exercise tolerance in patients presenting with a severely reduced DL_{CO} (*Study #2*). Thus, the interconnected goals of this thesis were: **1) to gain a deeper understanding of the physiological mechanisms underlying exertional symptoms (namely dyspnea and leg discomfort) and exercise intolerance in *f*-ILD of varied severity and 2) to explore the utility of DL_{CO} as a physiological biomarker of multiple systemic derangements which may jointly contribute to decrease exercise tolerance in this patient population.**

2.7.2 Objectives and Hypothesis

Study #1 (Chapter 3)

The primary objective of this study was to compare detailed physiological and perceptual responses to incremental exercise in *f*-ILD patients with largely preserved resting spirometry to healthy age- and sex-matched controls. We **hypothesized** that 1) *f*-ILD patients would have significantly elevated \dot{V}_E/\dot{V}_{CO_2} and dyspnea compared to controls and 2) the heightened dyspnea, \dot{V}_E/\dot{V}_{CO_2} , and diminished exercise tolerance in patients would be associated with the severity of DL_{CO} impairment.

Study #2 (Chapter 4)

Based on the findings from *Study #1*, we subsequently investigated the underpinnings of poor exercise tolerance in patients with a severely impaired DL_{CO} (<40% predicted). We **hypothesized** that these patients would have a greater burden of exertional symptoms (dyspnea and leg discomfort) and reduced exercise tolerance compared to healthy controls and their counterparts with lower DL_{CO} impairment, i.e., $\geq 40\%$ predicted.

Chapter 3

Physiological Underpinnings of Exertional Dyspnea in Mild Fibrosing Interstitial Lung Disease

A version of this study has previously been published in Respiratory Physiology and Neurobiology.

(See “Study #1 – Authorship Statement” & Appendix A)

(Smyth et al., 2023b)

3.1 Abstract

Background: The functional disturbances driving “*out-of-proportion*” dyspnea in patients with *f*-ILD and only mild restrictive abnormalities remain poorly understood.

Methods: 18 patients (10 with IPF) with preserved resting spirometry and mildly reduced total lung capacity ($\geq 70\%$ predicted) and 18 pairwise age-, sex-, and body mass index- (BMI) matched controls underwent an incremental CPET with measurements of operating lung volumes and Borg dyspnea scores.

Results: Patients’ lower exercise tolerance was associated with a higher \dot{V}_E/\dot{V}_{CO_2} ($\dot{V}_E/\dot{V}_{CO_{2nadir}} = 35 \pm 3$ versus 29 ± 2 ; $p < 0.001$). Patients showed higher tidal volume/inspiratory capacity and lower inspiratory reserve volume at a given exercise intensity, reporting higher dyspnea scores as a function of both work rate and \dot{V}_E . Steeper dyspnea-work rate slopes were associated with lower lung diffusion capacities, higher \dot{V}_E/\dot{V}_{CO_2} , and lower peak O_2 uptake ($p < 0.05$).

Conclusion: Heightened ventilatory demands in the setting of progressively lower capacity for tidal volume expansion on exertion largely explain the higher-than-expected dyspnea in *f*-ILD patients with largely preserved dynamic and “static” lung volumes at rest.

3.2 Introduction

f-ILD is an umbrella term encompassing any diffuse pulmonary parenchymal disease with tomographic features of fibrosis (distortion of the secondary lobule, reticulation, volume reduction, and traction bronchi(ol)ectasis) in patients at risk of developing progressive fibrosis (Cottin et al., 2019). The arrival of pharmacological strategies (i.e., antifibrotics) aimed at slowing disease progression and improving quality of life in IPF, the prototypical *f*-ILD (Torrise et al., 2017) has ignited new interest in the initial stages of the diseases (McCarthy & Keane, 2022). Due to the progressive nature of most *f*-ILDs (Cottin et al., 2019), the need for screening and earlier diagnosis has recently been emphasized (Valenzuela & Cottin, 2022). Improving our understanding of the sensory consequences of incipient/mild *f*-ILD has therefore become more clinically relevant in the past decade (McLean et al., 2021).

Preserved spirometry, with or without a mild reduction in TLC, is usually part of the mild *f*-ILD definition (Molina-Molina et al., 2018), justifying a “watchful waiting” approach rather than antifibrotic treatment in IPF (Torrise et al., 2017). In fact, most clinicians assume that it is unlikely that patients with no or only mild restriction would present with ventilatory abnormalities severe enough to elicit exertional dyspnea (Oldham et al., 2022). Thus, from the clinicians’ perspective, their complaints might be ascribed to simple deconditioning and/or the deleterious consequences of multiple co-morbidities in an elderly population (Cano-Jiménez et al., 2018). Since the symptom usually worsens with physical inactivity, they are eventually referred to the pulmonologist for further clarification of the mechanisms driving their “out-of-proportion” breathlessness.

There is, however, emerging evidence indicating a large variability in morbidity and mortality in IPF patients with a forced vital capacity (FVC) in the normal range (≥ 80 % predicted) (Albera et al., 2016; Bermudo et al., 2022). Further, a large subset of these patients report

significant activity-related dyspnea despite their apparently preserved ventilatory capacity (Bermudo et al., 2022; Oldham et al., 2022). Similar findings have been reported in other cases of *f*-ILD, such as sarcoidosis (Kallianos et al., 2015) and chronic hypersensitivity pneumonitis (Dias et al., 2018). Given that exertional dyspnea is thought to ultimately reflect a demand-capacity imbalance of the respiratory system (O'Donnell et al., 2019b), with consequential increases in the drive to breathe (Faisal et al., 2016; Schaeffer et al., 2018), it is conceivable that dyspneic patients with mild *f*-ILD show increased ventilatory requirements on exercise. In fact, increased wasted ventilation due to high physiological dead space has been reported in several *f*-ILD subtypes, including those with apparent mild disease (Marciniuk et al., 1994; Molgat-Seon et al., 2020). Moreover, patients reporting worse dyspnea on exertion typically present with a low DL_{CO}, suggesting poor gas exchange efficiency (Bermudo et al., 2022; Molgat-Seon et al., 2020) however, exertional dyspnea has yet to be linked to excess ventilation and a low DL_{CO} in *f*-ILD patients with largely preserved resting spirometry. If TLC and residual volume decrease in tandem to preserve FVC, the increase in V_T required to accommodate the heightened ventilatory demands may lead to earlier erosion of mechanical reserves (i.e., low inspiratory reserve volume) at reduced levels of physical activity (Faisal et al., 2016; Mendonca et al., 2014; Milne et al., 2020b). The corollary is that a high \dot{V}_E/\dot{V}_{CO_2} and coexistent mechanical constraints might jointly contribute to patients' disproportionate dyspnea on exertion.

The present study aimed to uncover the physiological underpinnings of exertional dyspnea in *f*-ILD patients with mild restrictive abnormalities on resting PFTs. We hypothesized that compared with pairwise sex-, age-, and BMI-matched controls, patients would a) ventilate in excess of metabolic demand during incremental CPET while b) breathing closer to TLC, indicating reduced inspiratory reserve volume and greater inspiratory constraints. Confirmation of these

hypotheses would indicate that ventilatory inefficiency elicits exertional dyspnea in *f*-ILD by increasing the ventilatory output while simultaneously reducing patients' ability to meet such heightened requirements.

3.3 Methods

3.3.1 Participants

This cross-sectional study included 18 participants followed in a multidisciplinary clinic specialized in the care of ILD patients at Queen's University, Kingston, Ontario, Canada. They were prospectively recruited to take part in studies reviewed for ethical compliance by the Queen's University Health Sciences and affiliated Teaching Hospital Research Ethics Board (Faisal et al., 2016; Marillier et al., 2021a; Milne et al., 2020b). We report data from the initial screening visits to assess eligibility for these studies, but there is no overlap with the current analysis. Patients were required to present with visually quantified "mild" fibrosis (Hansell et al., 2015) on a recent (within six months) high-resolution chest CT scan read by radiologists trained in the diagnosis and quantification of *f*-ILD.

Moreover, they should have an ILD where the fibrotic component might progress over time. In keeping with this *f*-ILD definition proposed by (Cottin et al., 2019), patients had IPF (n=10) (Lynch et al., 2018), nonspecific interstitial pneumonia (n = 4), connective tissue disease-related ILD (n=2), or sarcoidosis (n=2). As common denominators, they showed a) resting spirometric values within normal ranges, b) no evidence of pulmonary hypertension on a recent (within six months) transthoracic echocardiogram, c) absence of musculoskeletal abnormalities that could limit exercise tolerance, and d) no change in medication or exacerbations requiring oral or intravenous steroids in the eight weeks preceding study enrolment. No patient presented with incidental interstitial lung abnormalities as per Fleischner Society criteria (Hatabu et al., 2020).

Additionally, they did not fulfill the criteria for progressive-fibrosing ILDs (i.e., a relative decline in FVC \geq 10% and a relative decline in DL_{CO} \geq 15%, or a decline in FVC \geq 5% but $<$ 10% in combination with worsening of symptoms or radiographic findings in the preceding 24 months) (Cottin et al., 2018). Since it is highly prevalent in patients with IPF and other *f*-ILDs (Kumar et al., 2018) to improve the external validity of our results, we did not exclude patients with visually-quantified “mild” emphysema (Wille et al., 2016). Of note, however, no patient presented with radiographic abnormalities consistent with combined pulmonary fibrosis and emphysema (CPFE) (Cottin et al., 2005). 18 pairwise age-, sex-, and BMI-matched controls were also enrolled. This study has been reviewed for ethical compliance by the Queen’s University Health Science and affiliated Teaching Hospital’s Research Ethics Board (DMED-01659-13, see Appendix B).

3.3.2 Procedures

The modified 0-4 Medical Research Council (mMRC) classification graded participants’ activity-related dyspnea. PFTs (including dynamic and “static” lung volumes and DL_{CO}) were performed according to standard techniques, with the recorded values being compared to those established by the Global Lung Function Initiative (Hall et al., 2021; Quanjer et al., 2012; Stanojevic et al., 2017). Following current recommendations (Radtke et al., 2019), MVV was estimated as the forced expiratory volume in one second (FEV₁) x 40 (L/min). Incremental CPETs (10-20W increases every 2 minutes (min)) to symptom limitation were conducted on an electronically braked cycle ergometer with inspiratory capacity (IC) maneuvers at each work rate (Guenette et al., 2013). The intensities of the ventilatory output relative to its theoretical limits (submaximal \dot{V}_E /MVV ratio) (Milne et al., 2020a) were used as indexes of demand-capacity (im)balance of the respiratory system. As the rate of increase in V_T as a function of increasing \dot{V}_E may become blunted in the presence of higher inspiratory constraints, we determined the V_T - \dot{V}_E

inflection point (Phillips et al., 2021b) using the V-slope method (i.e. two lines of best fit starting from 1) rest; and 2) peak exercise to, where the intersection reflects the V_T - V_E inflection point) and modified Hey plots (i.e. V_E - V_T plots including data at every 30 second interval of exercise) (Hey et al., 1966). Borg leg discomfort and dyspnea ratings (0-10 category-ratio scale) were obtained at each work rate (Borg, 1982). Dyspnea scores at the highest equivalent work rate (60W) were compared to sex- and age-adjusted normative data, as established in our laboratory (Neder et al., 2020).

3.3.3 Statistical Analysis

A sample size of 18 patients with *f*-ILD and 18 controls was sufficient to detect the minimal clinically important difference of 1 Borg-unit in dyspnea at the highest equivalent work rate (60W) achieved by all participants (Faisal et al., 2016; Ries, 2005) (standard deviation (SD) = 1, α = 0.05 and β = 0.80). Although we *a priori* hypothesized that ventilatory inefficiency and inspiratory constraints were mechanistically linked to our primary outcome (exertional dyspnea), we did not power the study based on these variables, given the lack of data on their minimal clinically important difference. Unpaired t-tests were used to assess between group differences in participant characteristics, PFTs, and select CPET variables. A two-way repeated measure analysis of variance (ANOVA) with Bonferroni post hoc comparisons was used to evaluate the effect of group (fixed factor) on key dependent variables during incremental exercise (repeated factor). Pearson correlation was used to determine the association between continuous variables. Fisher's exact test was used to compare the frequency of subjects within different ranges of dyspnea intensity. Statistical significance was set *a priori* at $p < 0.05$.

3.4 Results

3.4.1 Participant Characteristics and Resting PFTs

Patients with *f*-ILD reported greater dyspnea in daily life compared with controls ($p < 0.001$) (Table 1). 11/18 (61.1 %) patients had a significant smoking history (>10 pack-years): 7 smokers showed trace-mild emphysema on chest CT. As per inclusion criteria, spirometric values were within normal ranges; however, patients had lower mean dynamic and “static” lung volumes compared with controls ($p < 0.05$). A mild restrictive pattern ($TLC \geq 70\%$ predicted $< LLN$) was observed in 13/18 (72.2%) patients as (F)VC was preserved due to proportional decreases in TLC and RV. Most patients (14/18, 77.7%) showed moderate reductions in DL_{CO} (40-60% predicted) and K_{CO} ($p < 0.01$; Table 1).

3.4.2 Peak Power and Metabolic/Cardiovascular Responses to Exercise

Patients with *f*-ILD showed a lower peak work rate and O_2 uptake ($\dot{V}O_{2\text{ peak}}$) compared with controls ($p < 0.01$). Given similar heart rates, peak O_2 pulse was lower in patients ($p < 0.05$). Oxygen uptake ($\dot{V}O_2$) at the lactate threshold tended towards being lower but was not statistically different (Table 2).

3.4.3 Gas Exchange/Ventilatory Responses to Exercise

Higher $\dot{V}_E/\dot{V}CO_2$ and lower end-tidal partial pressure for CO_2 ($P_{ET}CO_2$) were found at rest and throughout exercise in patients compared with controls ($p < 0.01$; Table 2 and Figure 2 A&B). At work rates $>20W$, patients had small but significant reductions in O_2 saturation by pulse oximetry (SpO_2) (Figure 2 C); of note, only a single patient showed an $SpO_{2\text{ peak}} < 90\%$. Patients’ heightened submaximal ventilation (Figure 3 A for \dot{V}_E and Figure 4 B&C for submaximal \dot{V}_E/MVV) was secondary to increased breathing frequency rather than a larger V_T (Figure 3 B&C as a function of work rate and Figure 5 B&C at iso \dot{V}_E). Given significantly lower IC at rest and

throughout exercise (Figure 3 D), V_T/IC was higher (Figure 3 E), and inspiratory reserve volume (IRV) was lower (Figure 3 F) in patients ($p<0.05$). Of note, the between-group differences in V_T/IC disappeared when expressed as a function of \dot{V}_E ; moreover, the $V_T-\dot{V}_E$ inflection point occurred at similar \dot{V}_E but significantly lower work rates in patients (Figure 5 D).

3.4.4 Sensory Responses to Exercise

Compared with controls, patients reported higher submaximal dyspnea scores at a given \dot{V}_E (Figure 5 A) and work rate (Figure 6 A). Moreover, they showed steeper dyspnea-work rate and dyspnea- \dot{V}_E slopes ($p<0.05$; Table 2). In keeping with a greater burden of exertional dyspnea in *f*-ILD (Neder et al., 2020), 11/18 (61%) patients rated their dyspnea intensity within the “very severe” range compared to only 2/18 (11%) controls who reached particularly high exercise intensities ($p<0.01$; Figure 6 B). Of note, dyspnea-work rate correlated negatively with DL_{CO} and $\dot{V}O_{2\text{ peak}}$ and positively with $\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$; moreover, these physiologic measurements correlated significantly with each other ($p<0.05$; Figure 7).

3.4.5 Putative Influence of Emphysema on Resting and Exercise Variables

As expected, we found lower DL_{CO} and K_{CO} in the subgroup of *f*-ILD patients with emphysema ($n = 7$) compared with their counterparts ($n = 11$) ($p<0.05$; Table 3); Emphysema-positive and -negative patients did not differ in exercise capacity, $\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$, V_T/IC and exertional dyspnea (Figure 8; $p>0.05$).

3.5 Discussion

We investigated the physiological underpinnings of exertional dyspnea in patients with *f*-ILD showing only mild restrictive abnormalities on resting lung function tests. Our main results were: a) despite spirometric values within normal ranges and normal to mildly reduced TLC, patients typically showed impaired gas exchange efficiency ($\downarrow DL_{CO}$); b) they ventilated in excess

of metabolic demand ($\uparrow \dot{V}_E/\dot{V}_{CO_2}$) showing only mild hypoxemia on exertion; c) patients' heightened submaximal ventilatory response was associated with increased demand capacity imbalance of the respiratory system as shown by lower submaximal breathing reserve ($\uparrow \dot{V}_E/MVV$) and restricted limits for V_T expansion (\downarrow IRV); and d) increased exertional dyspnea and reduced exercise tolerance were significantly related to lower DL_{CO} and higher \dot{V}_E/\dot{V}_{CO_2} . CPET findings showing excessive ventilation and inspiratory constraints on exertion despite modest abnormalities on dynamic and “static” lung volumes at rest might link mild *f*-ILD to exertional dyspnea, exposing potential therapeutic targets, such as the pulmonary microvasculature, to decrease the burden of this distressing symptom.

3.5.1 Excess Ventilation and Exertional Dyspnea in mild f-ILD

There is a marked similarity in the sources of increased afferent ventilatory stimulation during dynamic exercise in patients with cardiopulmonary diseases (Laviolette & Laveneziana, 2014). Heightened ventilation, in turn, is associated with increased neural drive to the inspiratory muscles, contributing to exertional dyspnea (James et al., 2022; Jolley et al., 2015; Milne et al., 2020b; Poon et al., 2007; Schaeffer et al., 2018; Stickland et al., 2022). In patients with *f*-ILD, vagally mediated reflexes triggered by lung-chest mechanoreceptors, increased wasted ventilation, gas exchange abnormalities, and peripheral ergoreceptor stimulation may all play a role (Schaeffer et al., 2018). In the current study, patients ventilated in excess of metabolic demands (Figure 2 A), decreasing the submaximal breathing reserve (Figure 4). Both higher demand (\uparrow submaximal \dot{V}_E ; Figure 3 A) and lower capacity (\downarrow MVV; Table 1) contributed to lower submaximal breathing reserve ($\uparrow \dot{V}_E/MVV$) in patients. Of note, they showed a faster rate of increase in \dot{V}_E compared to controls as exercise progressed; thus, the growing between-group differences in \dot{V}_E/MVV (Figure 4) may have contributed to the increase in dyspnea intensity seen at the later stages of exercise

(Figures 5 A & 6 A). Concomitantly, SpO₂ (Figure 2 C) and, conceivably, arterial PO₂ also diminished, likely further increasing the respiratory neural drive (Du Plessis et al., 2018). Due to the lack of arterial blood gas measurements, we were unable to detect the mechanisms driving a high \dot{V}_E/\dot{V}_{CO_2} ; for instance, patient's lower P_{ET}CO₂ (Figure 2 B) may have been secondary to a high physiological dead space, diluting expired PCO₂ and/or alveolar hyperventilation (Robertson, 2015). It should be noted that \dot{V}_E/\dot{V}_{CO_2} was increased at rest and minimal exertion (Figure 2 A); thus, excess ventilation was not a mere consequence of high lactic acidotic drive.

In normoxic to mildly hypoxemic patients (Figure 2 C) with minor fibrosis, a low DL_{CO} is more likely to reflect disturbances in \dot{V}_A/\dot{Q}_c matching rather than alveolar-capillary membrane thickening (Molgat-Seon et al., 2020). Given the spatial heterogeneity in lung inflammation and fibrosis (Weatherley et al., 2019) coupled with large variability in destruction, obstruction, and compression of the pulmonary capillaries in *f*-ILD (Farkas et al., 2011), \dot{V}_A/\dot{Q}_c mismatching (Read & Williams, 1959) may reduce DL_{CO} (Weatherley et al., 2021) and increase the fraction of V_T wasted by physiologic dead space. In fact, there is emerging evidence from functional magnetic resonance imaging (Weatherley et al., 2021) favoring increased regional perfusion heterogeneity in IPF patients with largely preserved FVC but moderately reduced DL_{CO} (Torres et al., 2022), again consistent with spatially heterogeneous vascular remodeling (Farkas & Kolb, 2011). Despite the likely contribution of the “vascular signal” for the high submaximal \dot{V}_E (Hansen & Wasserman, 1996), it is noteworthy that our patients did not present with pulmonary hypertension at rest, though this does not exclude some contribution of heightened pulmonary vascular pressure on exertion (J. A. Neder et al., 2022b). Given the low burden of emphysema and the absence of a significant effect on the key physiologic sensory responses (Table 3 and Figure 8), it seems

unlikely that our results were markedly influenced by emphysematous destruction of the alveolar-capillary membrane.

3.5.2 *The Role of Mechanical Constraints in the Genesis of Exertional Dyspnea in mild f-ILD*

Between-group statistically significant differences in FVC and FEV₁ were largely a result of “supra-normal” values in the controls (Table 1); thus, based on the most commonly available PFT to gauge disease severity, the accompanying clinician would be reluctant to mechanistically link f-ILD to patients’ dyspnea. Despite FVC normalcy, increased mechanical loading in the setting of higher ventilatory demands are likely to increase the neural drive to breathe and, consequently, exertional dyspnea (Faisal et al., 2016; Schaeffer et al., 2018). In fact, patients demonstrate less than normal room for tidal expansion from rest (Figure 3 D-F) and, conceivably require, higher inspiratory muscle work to overcome low lung compliance at a given V_T and \dot{V}_E (Table 2 and Figure 5 A). Thus, breathlessness was not a mere consequence of higher submaximal \dot{V}_E , indicating that the mechanical abnormalities did contribute to symptom severity (Neder et al., 2020) and greater inspiratory muscle activation was required to generate a given \dot{V}_E . The comparison of reported dyspnea scores with reference values was particularly informative as it properly considered the marked influence of sex and age on exercise-induced breathlessness (O'Donnell et al., 2019b). Interestingly, patients were more likely to report dyspnea scores above the 75th centile (“very severe” range) (Figure 6 B), a threshold which consistently pointed towards high \dot{V}_E/\dot{V}_{CO_2} , greater inspiratory constraints and worse exercise tolerance in our previous validation study (Neder et al., 2020). The V_T inflection point – signaling encroachment of critically-high inspiratory constraints (James et al., 2022) – occurred at a similar \dot{V}_E in patients and controls. Given the higher \dot{V}_E/\dot{V}_{CO_2} , such \dot{V}_E was reached at ~35% lower exercise intensity (Figure 5 D), again keeping with the notion that high submaximal \dot{V}_E accelerated the decline in IRV as

exercise progressed. It is conceivable that to mitigate the rate of increase in V_T/IC and the attending respiratory sensations, the heightened submaximal ventilatory requirements were met mainly via increased breathing frequency (Figures 3 B & 5 B); thus, ventilatory inefficiency contributed to exertional dyspnea dually: a) by increasing the ventilatory output $\uparrow \dot{V}_E/MVV$ (Figure 4) while b) eroding the diaphragm/respiratory muscle's ability to meet such high demands ($\uparrow V_T/IC$, $\downarrow IRV$) (Figure 3 E-F).

3.5.3 Clinical Implications

Normal to near normal lung volumes in patients with minor radiographic features of *f*-ILD is often thought to indicate “mild” disease, unlikely to trigger limiting breathlessness and exercise intolerance. However, our data indicate that relatively modest reductions in dynamic lung volumes, even if not large enough to decrease FVC below the lower limit (LLN) of normal, increases the likelihood of a (mildly) reduced TLC. The association of mildly reduced TLC and IC alongside a low DL_{CO} and exercise ventilatory inefficiency should be clinically valued as they allude to important mechanical constraints on exertion and activity-related dyspnea. An incremental CPET can also be useful to exclude other common causes of exercise intolerance in this elderly population, such as comorbid cardiac disease, obesity, and deconditioning. Jointly, these assertions highlight the importance of more advanced PFTs and CPET beyond simple spirometry in the longitudinal management of *f*-ILD patients in the initial stages of the disease. From a therapeutic perspective, it remains to be determined whether carefully selected patients with preserved FVC showing the above combinations of abnormalities are more likely to derive clinical benefit from antifibrotic treatment to slow the rate of decline in TLC and IC, mitigating the progression of dyspnea and exercise intolerance. Moreover, to the extent that attenuated pulmonary microvascular blood flow disruption can, at least partially, explain reduced DL_{CO} and ventilatory efficiency in

mild *f*-ILD (Farkas & Kolb, 2011; Torres et al., 2022; Weatherley et al., 2021), targeted interventions such as inhaled vasodilators (Phillips et al., 2021a) deserves scrutiny in the quest to improve long term clinical outcomes. In any circumstance, exercise reconditioning is likely useful to decrease afferent ventilatory stimulation (Vogiatzis & Zakynthinos, 2013), an effect that might be magnified by O₂ supplementation during the training sessions, even in patients who do not fulfill the criteria for long-term O₂ therapy (Anderson & Bye, 1984).

3.5.4 Study Limitations and Future Directions

We exposed the physiological underpinnings of exertional dyspnea (ventilatory inefficiency and inspiratory constraints) in mild *f*-ILD; however, additional studies with measurements of esophageal and gastric pressures and IND are warranted to clarify the proximate mechanism(s). By design, we assessed a group of patients referred to specialist care due to exertional dyspnoea. However, they are representative of the typical *f*-ILD population seen for elucidation of disproportionate dyspnea: elderly subjects, most commonly men with a smoking history, showing only mild structural abnormalities and normal/near normal dynamic and “static” lung volumes (O'Donnell et al., 2019b). It would have been interesting to contrast non-dyspneic *f*-ILD patients presenting with similar resting functional abnormalities, though, in practice, it is unlikely that the groups could be matched by the severity of DL_{CO} impairment (Molgat-Seon et al., 2020). There is a wide variability in the likelihood of disease progression depending on the specific etiology of *f*-ILD, with gas exchange and mechanical abnormalities progressing at different rates (Marciniuk & Gallagher, 1994). Given the assessment of patients showing similar levels of restriction and mild fibrosis across diseases, this does not seem a critical limitation in our transversal study. In keeping with a clinical physiology mechanistic study, our sample size was not particularly large. It should be noted, however, it allowed us to properly investigate any

between-group difference in exertional dyspnea, our primary outcome. It is conceivable that the abnormalities herein reported would be magnified by the intervening effects of extensive emphysema (Costa et al., 2020), a hypothesis that deserves further investigation. Between-sex differences in exercise physiology (Sheel et al., 2004) and a greater burden of dyspnea in elderly women (Cory et al., 2015; Neder et al., 2020) may potentiate the respiratory sensory consequences of the gas exchange and mechanical abnormalities caused by *f*-ILD. Larger studies with a higher number of women are therefore warranted.

3.6 Conclusion

Ventilatory inefficiency ($\uparrow\dot{V}_E/\dot{V}_{CO_2}$) increases the submaximal ventilatory output ($\uparrow\dot{V}_E/MVV$) while eroding the diaphragm/respiratory muscle's capacity to meet such high demands ($\uparrow V_T/IC$, $\downarrow IRV$). Both conspiring to increase exertional dyspnea in patients with *f*-ILD and only mild restrictive ventilatory abnormalities. The corollary is increased demand-capacity imbalance translated into increased attendant respiratory sensations and poor exercise tolerance. By incorporating these findings in the clinical interpretation of CPET, the reader can causally link apparently mild *f*-ILD to exertional dyspnea in individual patients while exposing the pulmonary microvasculature as a potential therapeutic target.

Table 1: Participant characteristics and resting pulmonary function data. (*Chapter 3*)

Variables	Controls (n=18)	f-ILD (n=18)
Participant Characteristics		
Sex, n (males / females)	13 / 5	13 / 5
Age, years	72 ± 6	72 ± 8
Height, cm	170.7 ± 8.4	169.4 ± 7.5
Weight, kg	79.1 ± 12.2	83.6 ± 14.7
BMI, kg/m ²	27.1 ± 3.1	29.0 ± 3.0
Smoking history, pack-years	1 ± 1	22 ± 20 *
mMRC 0-4, median (range)	0 (0-2)	1 (0-3) *
≥ 1, n	2	16 *
Lung Function		
FEV ₁ , L (% predicted)	2.7 ± 0.7 (99.6 ± 17.7)	2.4 ± 0.5 (88.5 ± 11.9) *
FVC, L (% predicted)	4.0 ± 1.0 (107.7 ± 15.5)	3.3 ± 0.6 * (92.0 ± 11.1) *
VC, L (% predicted)	4.2 ± 0.9 (105.9 ± 12.5)	3.4 ± 0.6 * (88.7 ± 10.2) *
FEV ₁ /FVC, %	70 ± 8	73 ± 5
TLC, L (% predicted)	6.0 ± 1.0 (96.3 ± 9.9)	4.8 ± 0.8 * (78.6 ± 7.3) *
≥ 70% predicted, n	18	18
≥ LLN, n	18	5
IC, L (% predicted)	3.2 ± 0.8 (114.5 ± 19.1)	2.5 ± 0.5 * (89.6 ± 11.2) *
FRC, L (% predicted)	2.8 ± 0.7 (82.3 ± 16.2)	2.3 ± 0.5 * (71.0 ± 13.3) *
RV, L (% predicted)	1.9 ± 0.6 (81.3 ± 22.0)	1.5 ± 0.4 * (65.7 ± 18.7) *
IC/TLC, %	53 ± 8	51 ± 7
FRC/TLC, %	47 ± 8	49 ± 7
RV/TLC, %	32 ± 8	31 ± 6
DL _{CO} , mL/min/mmHg (% predicted)	19.7 ± 4.6 (86.0 ± 17.9)	11.7 ± 2.8 * (51.5 ± 10.1) *
K _{CO} , mL/min/mmHg (% predicted)	3.9 ± 0.9 (97.5 ± 22.0)	2.8 ± 0.5 * (68.6 ± 12.2) *
MVV, L/min	95.8 ± 24.3	84.1 ± 16.2

Values are mean ± SD. *Definition of abbreviations:* f-ILD: fibrosing interstitial lung disease; BMI: body mass index; mMRC: modified Medical Research Council; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; VC: vital capacity; TLC: total lung capacity; LLN: lower limit of normal; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; DL_{CO}: diffusion capacity of the lung for carbon monoxide; MVV: maximal voluntary ventilation. **p*<0.05.

Table 2: Selected cardiopulmonary and sensory responses to incremental exercise. (*Chapter 3*)

Variables	Controls (n=18)	f-ILD (n=18)
Power		
Work Rate , W (% predicted)	135 ± 38 (112 ± 24)	88 ± 17 * (74 ± 14) *
Metabolic/cardiovascular		
$\dot{V}O_{2\text{ peak}}$, L/min (% predicted)	2.07 ± 0.65 (108 ± 24)	1.51 ± 0.41 * (78 ± 17) *
$\dot{V}O_2$ at the LT, % predicted $\dot{V}O_{2\text{ max}}$	72.2 ± 29.6	56.9 ± 19.2
RER	1.13 ± 0.09	1.13 ± 0.11
Heart rate, beats/min	139 ± 21	127 ± 22
O ₂ pulse, mL/beat	15 ± 4	12 ± 2 *
Gas exchange		
$\dot{V}_E/\dot{V}CO_2$	33.5 ± 2.8	38.5 ± 5.5 *
$\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$	29 ± 2	35 ± 3 *
≥ 34, n	0	13 *
$P_{ET}CO_2$, mmHg	33.5 ± 2.8	31.1 ± 3.5 *
≤ 35 at $\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$, n	8	13 *
SpO ₂ , %	96 ± 3	93 ± 2 *
SpO _{2 peak-rest} , %	-1 ± 3	-3 ± 2 *
Ventilatory		
\dot{V}_E , L/min	78.5 ± 25.2	65.4 ± 19.1
V_T , L	2.13 ± 0.54	1.77 ± 0.37 *
f_B , Breaths/min	37 ± 7	37 ± 10
IC, L	2.98 ± 0.69	2.44 ± 0.53 *
Δ IC from rest, L	-0.05 ± 0.56	-0.04 ± 0.35
V_T/IC , %	72 ± 9	75 ± 9
IRV, L	0.85 ± 0.35	0.63 ± 0.30
Sensory		
Dyspnea, Borg units	5.2 ± 2.6	5.9 ± 2.3
Leg discomfort, Borg units	5.5 ± 2.7	6.1 ± 2.3
Dyspnea-work rate slope, Borg units/W	0.04 ± 0.02	0.07 ± 0.03 *
Dyspnea- \dot{V}_E slope, Borg units/L/min	0.05 ± 0.04	0.10 ± 0.08 *

Data at peak exercise unless otherwise specified. Values are mean ± SD. *Definition of abbreviations:* f-ILD: fibrosing interstitial lung disease; $\dot{V}O_2$: oxygen uptake; $\dot{V}O_{2\text{ peak}}$: peak measured oxygen uptake; $\dot{V}O_{2\text{ max}}$: maximum oxygen uptake attainable; LT: lactate threshold; RER: respiratory exchange ratio; \dot{V}_E : expired minute ventilation; $\dot{V}CO_2$: carbon dioxide output; $P_{ET}CO_2$: end-tidal partial pressure for carbon dioxide; SpO₂: oxygen saturation by pulse oximetry; V_T : tidal volume; f_B : breathing frequency; IC: inspiratory capacity; IRV: inspiratory reserve volume. * $p < 0.05$.

Table 3. Selected participant characteristics, lung function, and incremental CPET variables in *f*-ILD patients with and without CT-confirmed emphysema (a sub analysis). (*Chapter 3*)

Variables	Controls (n=18)	<i>f</i>-ILD Without emphysema (n=11)	<i>f</i>-ILD With emphysema (n=7)
Participant Characteristics			
Sex, n (males / females)	13 / 5	7/4	6/1
Age, years	72 ± 6	73 ± 6	71 ± 9
BMI, kg/m ²	27.1 ± 3.1	29 ± 3	29 ± 5
Smoking history, pack-years	1 ± 1	15 ± 19 *	31 ± 17 *
mMRC 0-4, median (range)	0 (0-2)	2 (0-3)*	1 (0-3) *
≥ 1, n	2	10 *	6 *
Lung Function			
FEV ₁			
L	2.7 ± 0.7	2.3 ± 0.5	2.5 ± 0.4
% predicted	99.6 ± 17.7	88.7 ± 11.8	88.1 ± 11.2
FVC			
L	4.0 ± 1.0	3.1 ± 0.6 *	3.6 ± 0.5
% predicted	107.7 ± 15.5	90.7 ± 10.0 *	94.0 ± 11.6 *
VC			
L	4.2 ± 0.9	3.2 ± 0.6 *	3.6 ± 0.5 *
% predicted	105.9 ± 12.5	88.1 ± 9.2 *	89.6 ± 10.9 *
FEV ₁ /FVC, %	70 ± 8	75 ± 5	71 ± 4
FEF ₂₅₋₇₅			
L/sec	1.7 ± 1.0	1.7 ± 0.6	1.6 ± 0.2
%predicted	75.8 ± 34.2	82.8 ± 30.2	73.8 ± 10.9
TLC			
L	6.0 ± 1.0	4.6 ± 0.7 *	5.2 ± 0.6
% predicted	96.3 ± 9.9	77.5 ± 7.4 *	80.4 ± 6.3 *
≥ 70% predicted, n	18		
≥ LLN, n	18		
IC/TLC, %	53 ± 8	53 ± 7	48 ± 5
RV/TLC, %	32 ± 8	31 ± 7	30 ± 4
V _A /TLC, %	85 ± 10	85 ± 10	88 ± 7
DL _{CO}			
mL/min/mmHg	19.7 ± 4.6	11.5 ± 3.1 *	11.9 ± 2.1 *
% predicted	86.0 ± 17.9	52.1 ± 11.0 *	50.5 ± 7.3 *
K _{CO}			
mL/min/mmHg	3.9 ± 0.9	2.9 ± 0.6 *	2.6 ± 0.2 *
% predicted	97.5 ± 22.0	71.5 ± 13.3 *	64.1 ± 7.3 *
Power			
Work Rate			
W	134 ± 38	86 ± 18 *	89 ± 16 *
% predicted	112 ± 24	76 ± 10 *	70 ± 16 *
Metabolic/Cardiovascular			

$\dot{V}O_2$			
L/min	2.07 ± 0.63	1.43 ± 0.37 *	1.64 ± 0.40
% predicted	107.6 ± 23.2	77.7 ± 16.4 *	79.2 ± 16.1 *
Gas Exchange			
$\dot{V}_E/\dot{V}CO_2$ nadir	29.5 ± 2.0	35.3 ± 3.1 *	37.4 ± 1.8 *

Values are mean ± SD. *Definitions of abbreviations:* *f*-ILD: fibrosing interstitial lung disease; BMI: body mass index; mMRC: modified Medical Research Council; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; SVC: slow vital capacity; FEF₂₅₋₇₅: forced expiratory flow at 25-75% of the forced vital capacity; TLC: total lung capacity; IC: inspiratory capacity; RV: residual volume; DL_{CO}: diffusion capacity of the lung for carbon monoxide; V_A: alveolar volume; K_{CO}: transfer coefficient for carbon monoxide; $\dot{V}O_2$: volume of oxygen consumption in one minute; expired minute ventilation (\dot{V}_E) relative to the volume of carbon dioxide produced in one minute ($\dot{V}CO_2$). * $p < 0.05$ for *f*-ILD versus control. † $p < 0.05$ *f*-ILD with versus without emphysema.

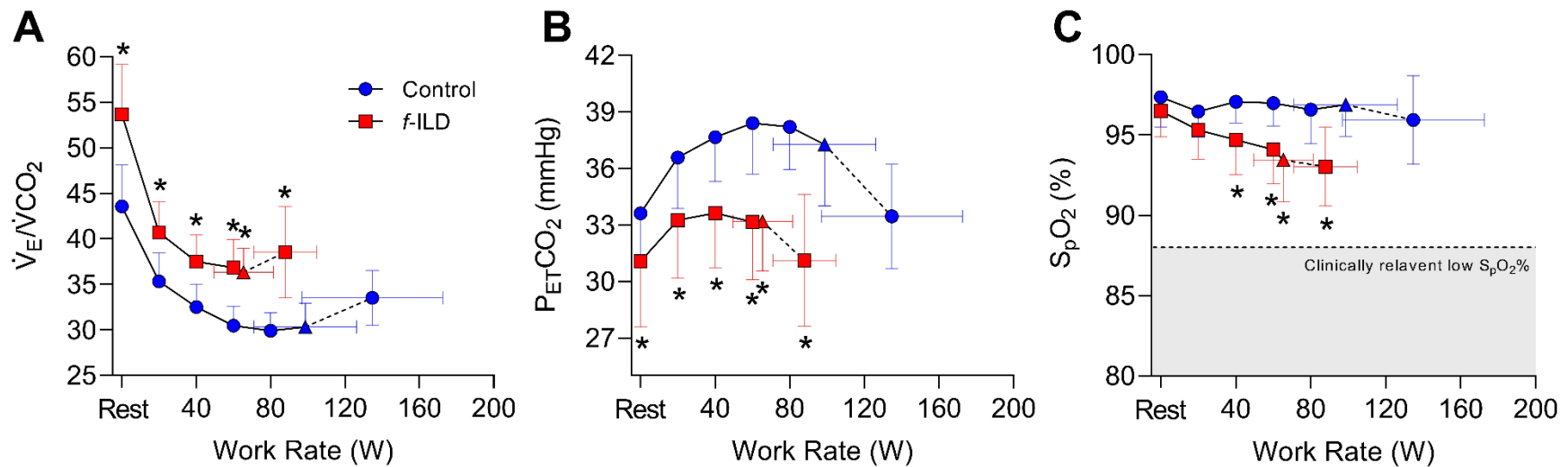


Figure 2. Ventilatory and gas exchange responses to incremental exercise. (*Chapter 3*)

(A) Expired minute ventilation (\dot{V}_E) relative to carbon dioxide output (\dot{V}_{CO_2}); (B) end-tidal partial pressure for carbon dioxide ($P_{ET}CO_2$); and (C) oxygen saturation by pulse oximetry (S_pO_2) relative to increasing work rate (W) during incremental exercise in patients with *f*-ILD ($n = 18$; red squares) and pairwise age- and sex-matched healthy controls ($n = 18$; blue circles). Shaded area shown in C) indicates the clinically relevant low S_pO_2 of 88% (Raghu et al., 2011). Triangles represent the V_T - \dot{V}_E inflection point. Data are mean \pm SD. * $p < 0.05$.

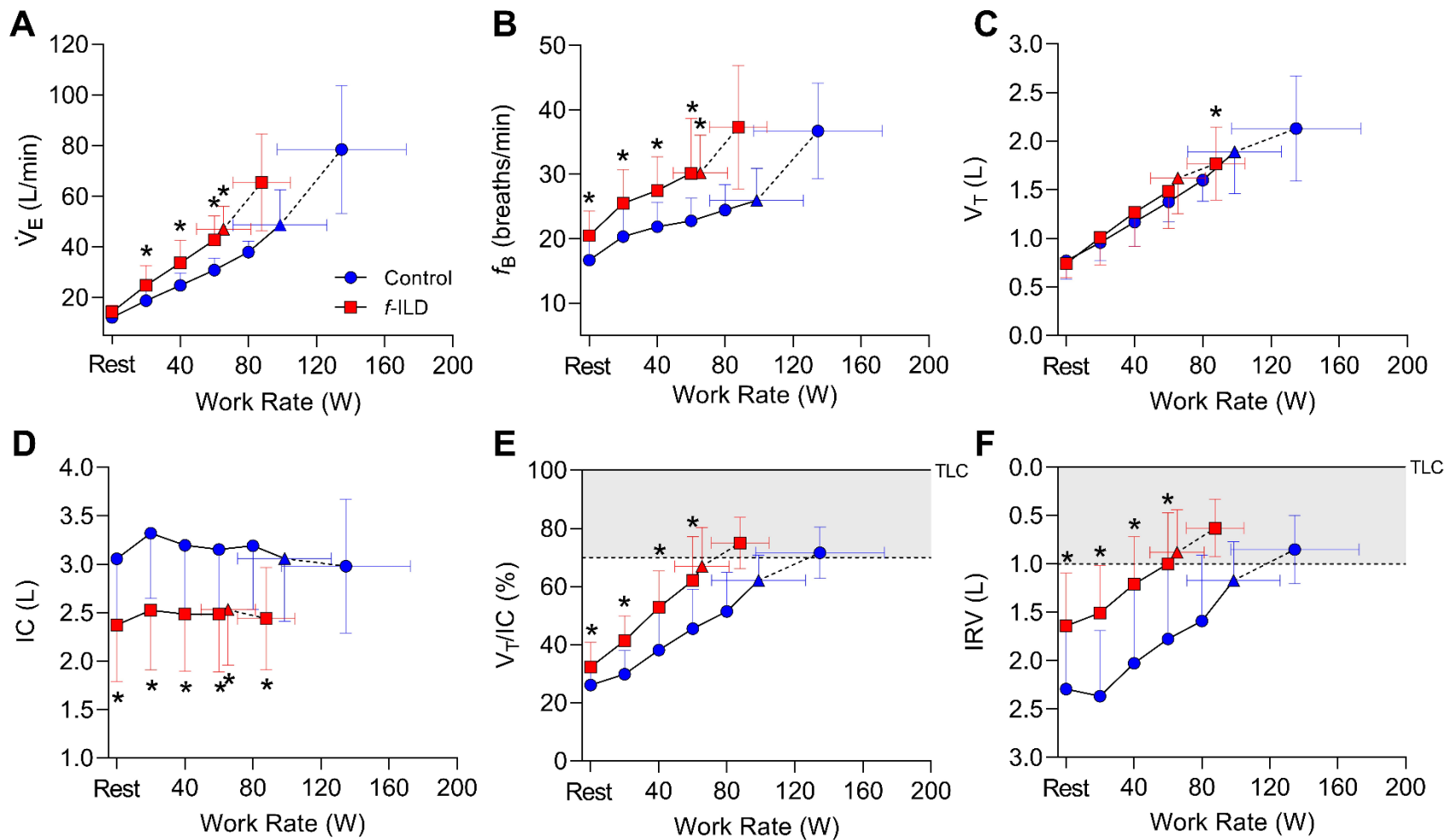


Figure 3. Ventilatory, breathing pattern, and operating lung volume responses to incremental exercise. (*Chapter 3*)

(**A**) Expired minute ventilation (\dot{V}_E); (**B**) breathing frequency (f_B); (**C**) tidal volume (V_T); (**D**) inspiratory capacity (IC); (**E**) V_T as a fraction of IC (V_T/IC %); (**F**) inspiratory reserve volume (IRV) relative to increasing work rate (W) during incremental exercise in patients with *f*-ILD ($n = 18$; *red squares*) and pairwise age- and sex-matched healthy controls ($n = 18$; *blue circles*). Shaded areas in *E*) and *F*) indicate previously established thresholds for critical inspiratory constraint associated with exertional dyspnea (Guenette et al., 2013). *Triangles* represent the V_T - \dot{V}_E inflection point. Data are mean \pm SD. * $p < 0.05$.

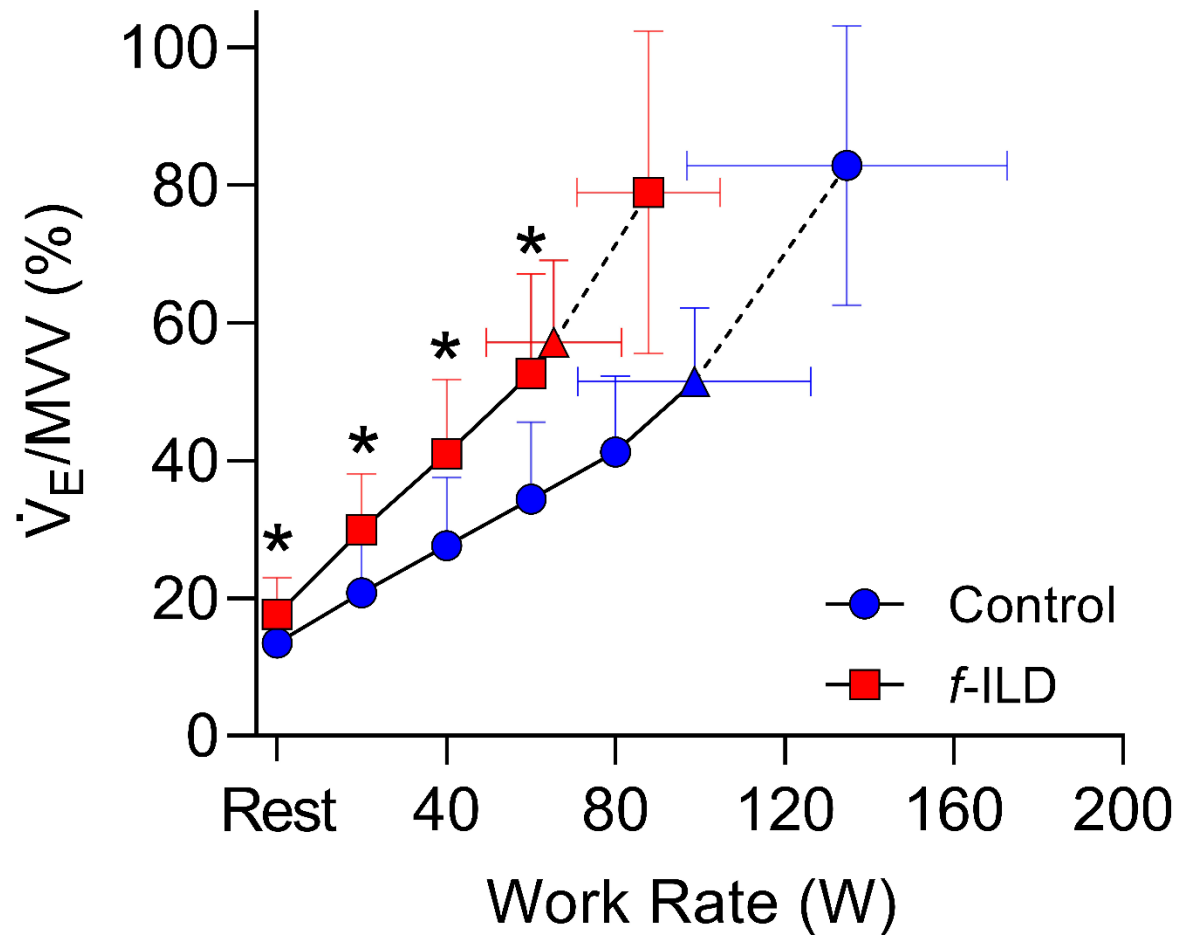


Figure 4. Ventilatory reserve during incremental exercise. (Chapter 3)

High expired minute ventilation (\dot{V}_E) / maximal voluntary ventilation (MVV) (i.e., low submaximal breathing reserve) during incremental exercise in patients with *f*-ILD (n = 18; *red squares*) and pairwise age- and sex-matched healthy controls (n = 18; *blue circles*). *Triangles* represent the V_T - \dot{V}_E inflection point. Data are mean \pm SD. * $p < 0.05$.

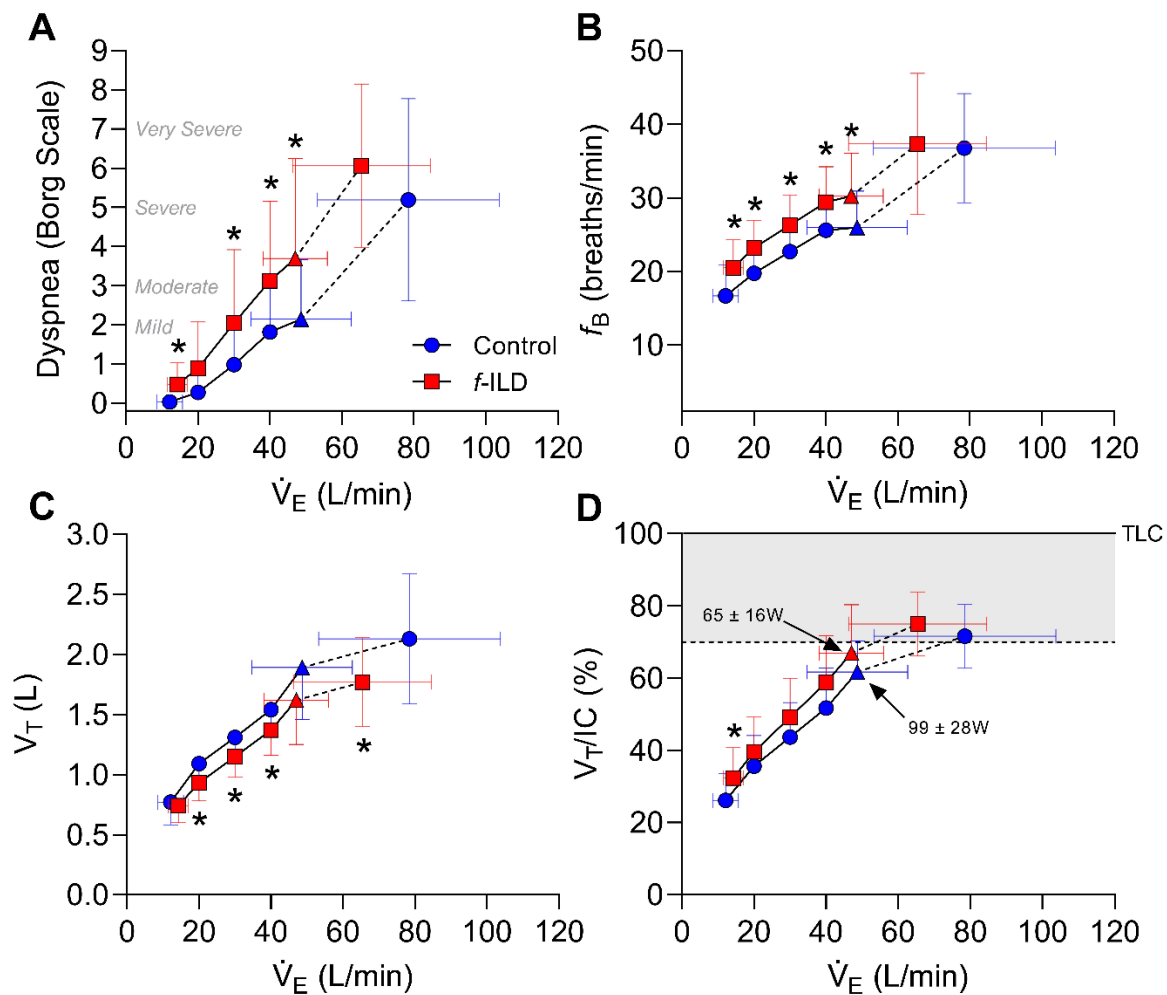


Figure 5. Dyspnea, breathing pattern, and operating lung volumes relative to increasing \dot{V}_E during incremental exercise. (*Chapter 3*)

(**A**) Borg dyspnea scores; (**B**) breathing frequency (f_B); (**C**) tidal volume (V_T); (**D**) V_T /inspiratory capacity (IC) relative to expired minute ventilation (\dot{V}_E) during incremental exercise in patients with *f*-ILD ($n = 18$; *red squares*) and pairwise age- and sex-matched healthy controls ($n = 18$; *blue circles*). Shaded area in **D**) indicates previously established thresholds for critical inspiratory constraint associated with exertional dyspnea (Guenette et al., 2013). *Triangles* represent the V_T - \dot{V}_E inflection point. Data are mean \pm SD. * $p < 0.05$.

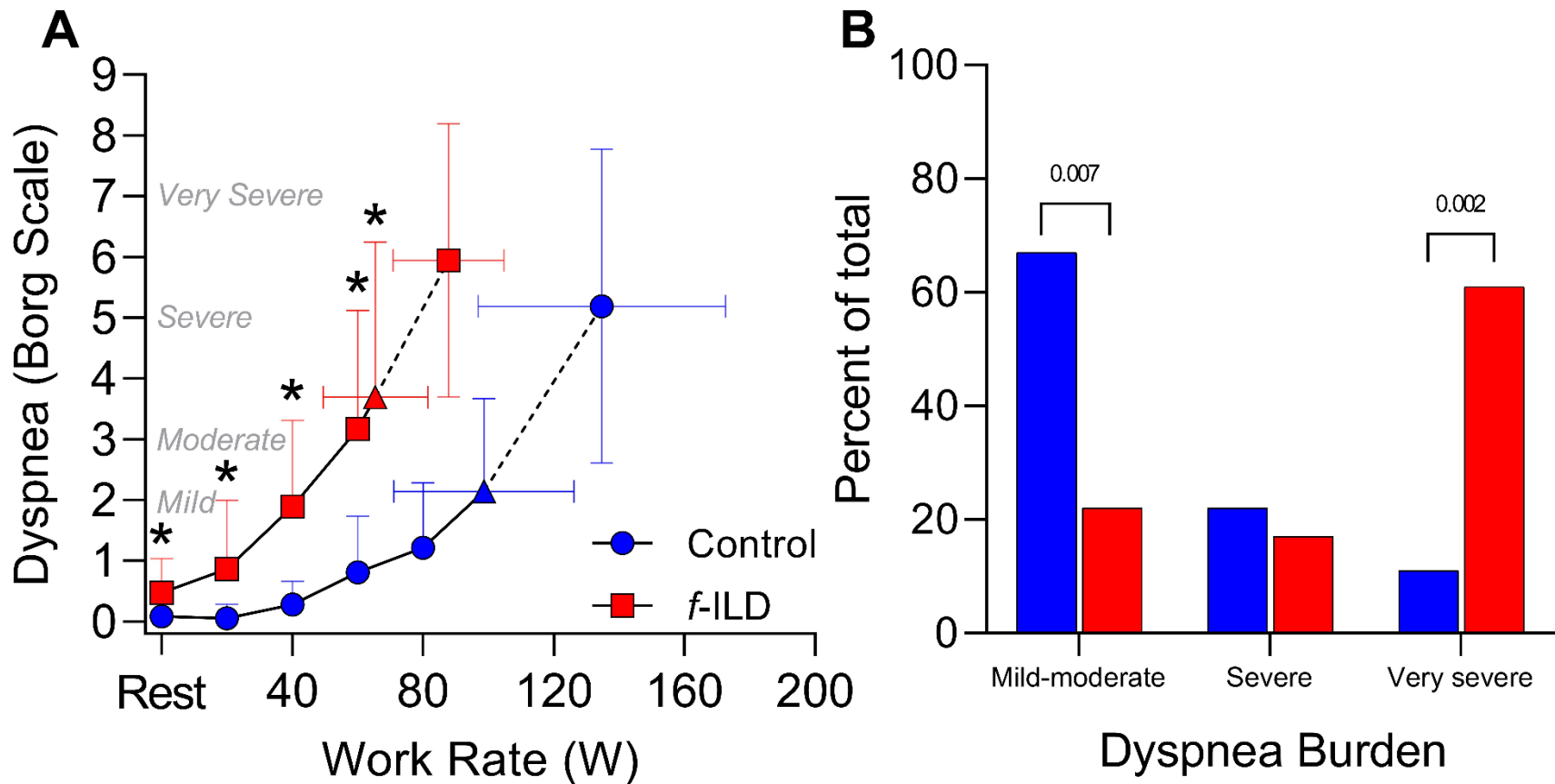


Figure 6. Dyspnea scores during incremental exercise. (*Chapter 3*)

(**A**) Borg dyspnea scores during incremental exercise relative to increasing work rate (W) in patients with *f*-ILD (n = 18; *red squares*) and pairwise age- and sex-matched healthy controls (n = 18; *blue circles*); (**B**) shows dyspnea ratings at the highest equivalent work rate (60W) related to ranges of severity as established by normative data (Neder et al., 2020). *Triangles* in (**A**) represent the V_T-V_E inflection point. Data are mean ± SD. * *p*<0.05.

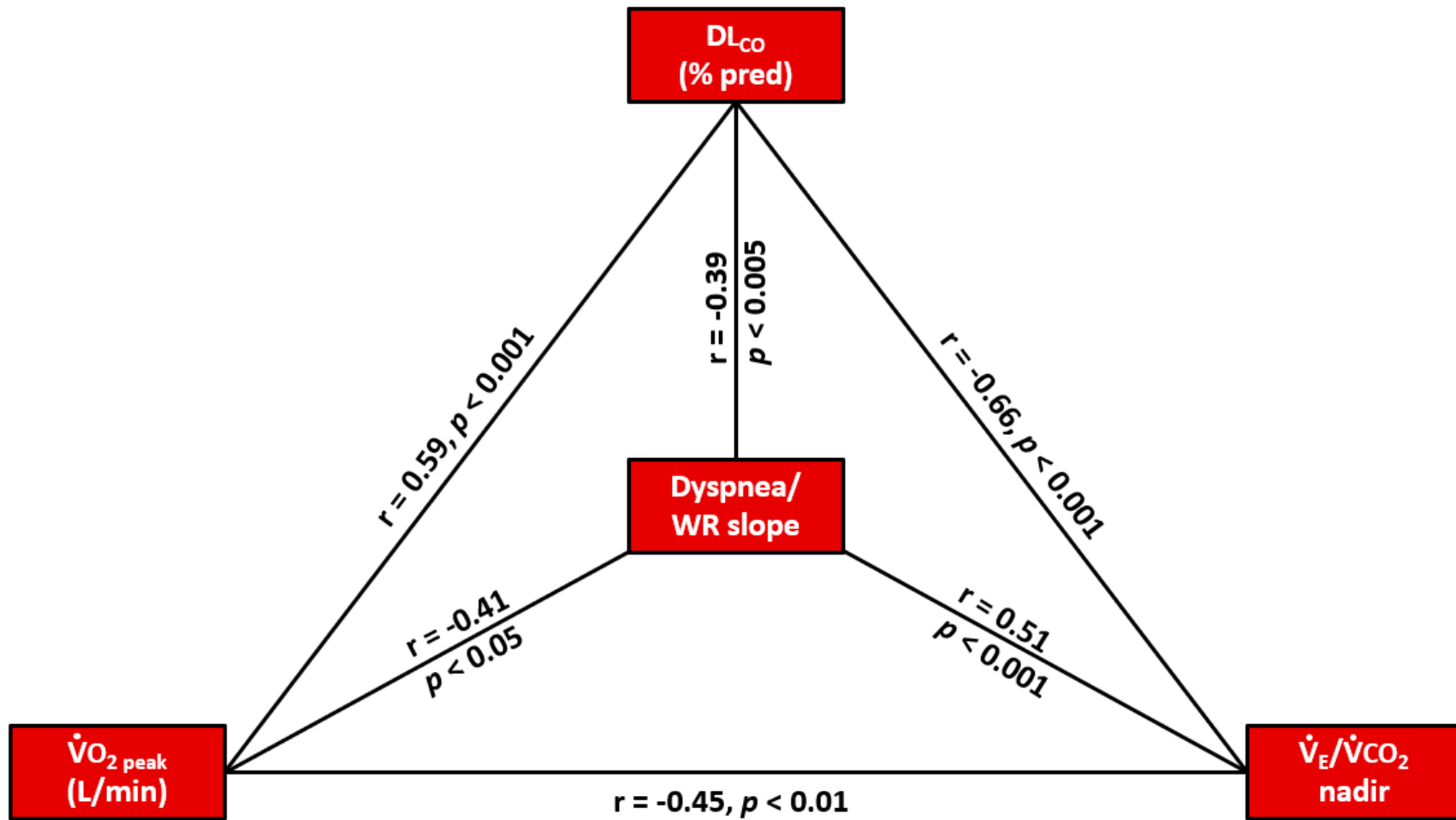


Figure 7. Relationship between Dyspnea-work rate, DLCO, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$ nadir. (Chapter 3)

Significant cross-correlations among work rate (WR)-corrected Borg dyspnea scores, resting diffusion capacity of the lung for carbon monoxide (DLCO), nadir exercise expired minute ventilation (\dot{V}_E)/carbon dioxide output ($\dot{V}CO_2$), and peak oxygen uptake ($\dot{V}O_2$) in patients with *f*-ILD (n = 18).

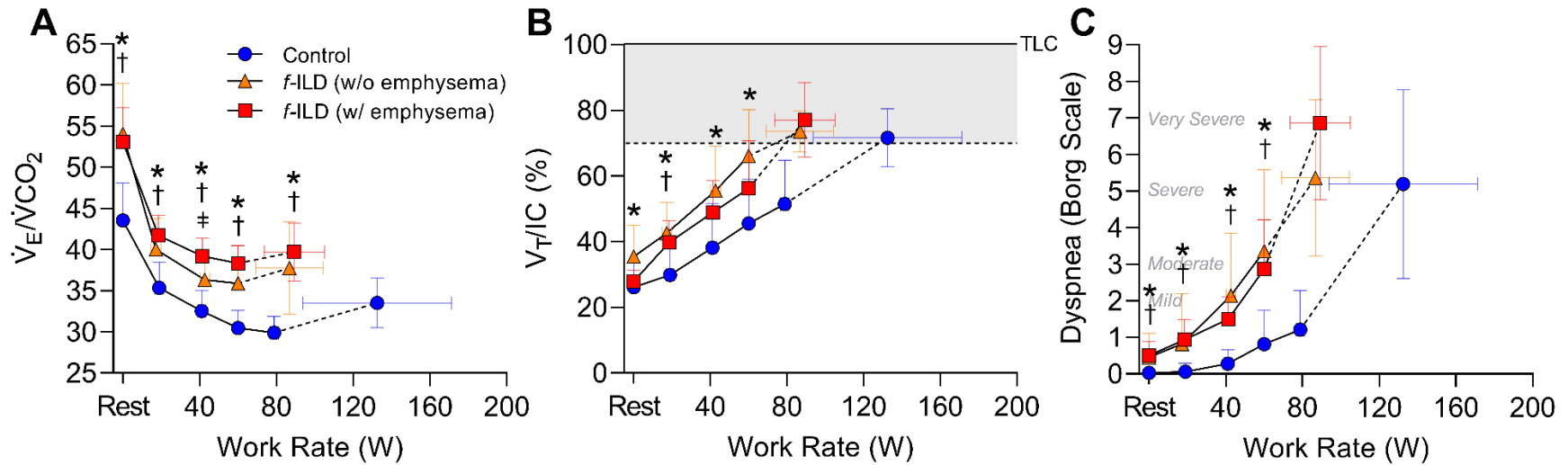


Figure 8. Ventilatory, gas exchange, operating lung volume, and dyspnea responses to incremental exercise in *f*-ILD patients with and without emphysema. (*Chapter 3*)

(**A**) Expired minute ventilation (\dot{V}_E) relative to carbon dioxide production (\dot{V}_{CO_2}); (**B**) Tidal volume (V_T)/inspiratory capacity (IC) ratio; and (**C**) Borg dyspnea scores relative to increasing work rate in patients with *f*-ILD, both with emphysema ($n = 7$; *red squares*) and without emphysema ($n = 11$; *orange triangles*) and pairwise age- and sex-matched controls ($n = 18$, *blue circles*). Shaded area in C indicates previously established thresholds for critical inspiratory constraint associated with exertional dyspnea (Guenette et al., 2013). Data are mean \pm SD. * $p < 0.05$ controls vs *f*-ILD with emphysema; † $p < 0.05$ controls vs *f*-ILD without emphysema; ‡ $p < 0.05$ *f*-ILD with and without emphysema.

Chapter 4:

Systemic Determinants of Exercise Intolerance in Patients with Fibrosing Interstitial Lung Disease and a Severely Impaired DL_{CO}

A version of this study has previously been published in Respiratory Care.

(See “Study #2 - Authorship Statement” & Appendix C)

(Smyth et al., 2023a)

4.1 Abstract

Background: The precise mechanisms driving poor exercise tolerance in patients with *f*-ILD showing a severe impairment in DL_{CO}<40% predicted are not fully understood. Rather than only reflecting impaired O₂ transfer, a severely impaired DL_{CO} may signal deranged integrative physiologic adjustments to exercise, which jointly increases the burden of exertional symptoms in *f*-ILD.

Methods: Sixty-seven patients (46/67 with IPF, 24/67 showing DL_{CO}<40% predicted) and 22 controls underwent PFTs and an incremental CPET with serial measurements of operating lung volumes and 0-10 Borg dyspnea and leg discomfort scores.

Results: Patients from the DL_{CO}<40% predicted group showed lower spirometric values, more severe restriction, and a lower K_{CO} compared to controls and patients with less impaired DL_{CO} ($p<0.05$). Peak work rate was ~45% (versus controls) and ~20% (versus DL_{CO}≥40% predicted) lower in the DL_{CO}<40% predicted group, being associated with lower (and flatter) O₂ pulse, an earlier lactate (“anaerobic”) threshold, heightened submaximal ventilation, and lower O₂ saturation by pulse oximetry. Moreover, critically high inspiratory constraints were reached at lower exercise intensities in the DL_{CO}<40% predicted group ($p<0.05$). In association with the

greatest leg discomfort scores, they reported the highest dyspnea scores at a given work rate. Between-group differences lessened or disappeared when dyspnea intensity was related to indexes of increased demand-capacity imbalance (i.e., decreasing submaximal, dynamic ventilatory reserve, and inspiratory reserve volume/total lung capacity) ($p < 0.05$).

Conclusion: A severely reduced DL_{CO} in *f*-ILD signals multiple interconnected derangements (cardiovascular impairment, an early shift to anaerobic metabolism, excess ventilation, inspiratory constraints, and hypoxemia), which ultimately lead to limiting respiratory dyspnea and peripheral leg discomfort symptoms. $DL_{CO} < 40\%$ predicted, therefore, might help in clinical decision-making to identify the *f*-ILD patients who might derive particular benefit from pharmacological and nonpharmacological interventions aimed at lessening these systemic abnormalities.

4.2 Introduction

f-ILD is an umbrella term used to describe ILD in patients who, independent of the specific etiology, at some point in time, exhibit a progressive fibrosing phenotype (Cottin et al., 2018; Cottin et al., 2019). Longitudinal loss of lung function is part of the *f*-ILD definition, and most patients eventually decrease their daily activities due to poor exercise tolerance (Swigris et al., 2018). The consequence is a vicious circle of progressive disablement (Holland, 2010) and reduced quality of life (Chang et al., 1999). It is crucial, therefore, to identify PFT parameters that can be used in clinical practice to predict a high burden of activity-related symptoms and exercise intolerance in these patients (Molgat-Seon et al., 2019, 2020).

In this context, a severely impaired (<40% predicted) (Enright, 2016) DL_{CO} has long been recognized as a marker of disease progression across all *f*-ILD etiologies (see (Keogh & Crystal, 1980) for a classical review on the topic). The underlying mechanisms and their connection with clinical outcomes (i.e., activity-related symptoms), however, are still not fully understood. Although patients with markedly reduced DL_{CO} present with worse hypoxemia on exertion (Du Plessis et al., 2018; Molgat-Seon et al., 2019, 2020), there is wide variability in exercise tolerance and breathlessness at a given PaO₂ (Marciniuk et al., 1994; Schaeffer et al., 2019; Schaeffer et al., 2018). DL_{CO} is a metric of gas transfer that is strongly influenced by the “accessible” V_A (Kaminsky et al., 2007; Neder et al., 2019b) which, in turn, depends on the severity of the associated restriction, TLC decrement) (Keogh & Crystal, 1980) and potential heterogeneities in ventilation distribution (Agustí et al., 1991), decreasing the V_A/TLC ratio (Neder et al., 2019b). DL_{CO} does correlate well with the anatomical underpinnings of the disease (i.e., fibrosis severity) (Du Plessis et al., 2018; Molgat-Seon et al., 2019, 2020). Of note, a severely impaired DL_{CO} has been associated with exercise-related pulmonary hypertension in diffuse parenchymal lung disease

(Degani-Costa et al., 2015; Hansen & Wasserman, 1996; Panagiotou et al., 2017). Moreover, those with more pronounced abnormalities in skeletal muscle structure and function show particularly low DL_{CO} (Molgat-Seon et al., 2021; Panagiotou et al., 2016). The corollary is that $DL_{CO} < 40\%$ predicted might signal marked decrements in O_2 delivery to and utilization by the contracting skeletal muscles (Marillier et al., 2023a), contributing to increased neuromuscular (contractile) fatigue (Marillier et al., 2021b), an earlier lactate (“anaerobic”) threshold (Hansen & Wasserman, 1996), and, consequently, a heightened sensation of leg discomfort (Holland, 2010). It is conceivable, therefore, that rather than just reflecting impaired O_2 transfer across the alveolar-capillary membrane (Neder et al., 2019b), a severely reduced DL_{CO} is a marker of multiple interconnected respiratory and non-respiratory derangements which jointly interact to increase the burden of exertional symptoms and, consequently, exercise intolerance in *f*-ILD.

To explore this overarching hypothesis, we aimed to contrast the physiological (cardiovascular, skeletal muscle metabolism, ventilatory requirements, operating lung volumes, pulmonary gas exchange) and sensory (dyspnea and leg discomfort) responses to incremental exercise in *f*-ILD patients showing a severely impaired DL_{CO} versus those with mildly-to-moderately reduced DL_{CO} (i.e., $\geq 40\%$ predicted) and non-*f*-ILD healthy controls of similar sex and age distribution. We postulated that the lowest exercise tolerance shown by patients in the severely impaired DL_{CO} group ($< 40\%$ predicted) would be associated with; *i*) greater cardiovascular impairment, *ii*) an earlier “anaerobic” threshold, *iii*) heightened exertional ventilation, *iv*) more severe mechanical-inspiratory constraints, and *v*) worse exertional hypoxemia, leading to a greater cumulative burden of attendant *vi*) respiratory (dyspnea) and *vii*) non-respiratory (leg discomfort) sensations. Confirmation of the study hypothesis would provide a solid rationale for DL_{CO} as a key PFT parameter to expose the pulmonary and systemic consequences of *f*-ILD.

4.3 Methods

4.3.1 Participants

This was a cross-sectional study enrolling 67 participants followed in a multidisciplinary clinic specialized in the care of ILD patients at KHSC, Queen's University, Kingston, ON, Canada. They were prospectively recruited to take part in studies reviewed for ethical compliance by the Queen's University Health Sciences and affiliated Teaching Hospital Research Ethics Board (Faisal et al., 2016; Marillier et al., 2021a; Milne et al., 2020b). Data and participant informed consent were obtained during the initial screening visits to assess eligibility for these studies, but there is no overlap with the current analysis. All patients had radiographically defined ILD in which the fibrotic component might progress over time. In keeping with this *f*-ILD definition (Cottin et al., 2019), patients had IPF (n=46), nonspecific interstitial pneumonia (n=10), chronic hypersensitivity pneumonitis (n=4), autoimmune/connective tissue disease-related ILD (n=3), unclassifiable idiopathic interstitial pneumonia (n=2), and sarcoidosis (n=2). As common denominators, they showed a) no evidence of pulmonary hypertension in a recent (within six months) transthoracic echocardiogram, b) absence of musculoskeletal abnormalities which could limit exercise tolerance, and c) no change in medication or exacerbations requiring oral or intravenous steroids (or another anti-inflammatory therapy) in the eight weeks preceding study enrolment.

Since smoking is highly prevalent in patients with IPF and other *f*-ILDs (Cottin et al., 2018; Cottin et al., 2019) and to improve the external validity of our results, we did not exclude those with visually-quantified "mild" emphysema (Wille et al., 2016). To further minimize the confounding effects of extensive emphysema on DL_{CO}, no patient was included with radiographic abnormalities consistent with CPFE. 22 age- and sex-matched historical controls aged 40 or older

were also enrolled. This study has been reviewed for ethical compliance by the Queen’s University Health Science and affiliated Teaching Hospital’s Research Ethics Board (DMED-01659-13, see Appendix D).

4.3.2 Procedures

The 0-4 mMRC classification was used to grade participants’ activity-related dyspnea. PFTs (including dynamic and “static” lung volumes and single-breath DL_{CO}) were performed according to standard techniques and compared to reference values established by the Global Lung Function Initiative (Hall et al., 2021; Quanjer et al., 2012; Stanojevic et al., 2017). MVV was estimated as $FEV_1 \times 40$ (L/min). Incremental CPET to symptom limitation (10-20 W increases every 2 min) was conducted on an electronically braked cycle ergometer with dynamic inspiratory capacity (IC_{dyn}) measurements within the last 30-second interval of each work rate step (Guenette et al., 2013). The “anaerobic” threshold was identified based on the V-slope (\dot{V}_{CO_2} - \dot{V}_{O_2}) plot with corroboratory evidence from the standard ventilatory method (i.e., the \dot{V}_E/\dot{V}_{CO_2} - and \dot{V}_E/\dot{V}_{O_2} -Work rate inflection points). The \dot{V}_E/\dot{V}_{CO_2} relationship assessed ventilatory (in) efficiency, herein termed excess ventilation (J. A. Neder et al., 2022b). Arterial SO_2 was estimated by pulse oximetry. The intensity of the ventilatory output relative to its theoretical limits (dynamic ventilatory reserve (VR_{dyn})) was calculated as $(1 - (\text{submaximal } \dot{V}_E / MVV)) \times 100$ (Berton et al., 2023). The severity of mechanical constraints to tidal volume expansion were calculated based on the V_T/IC_{dyn} , end-inspiratory lung volume (EILV), and IRV/TLC ratios (Guenette et al., 2013). Since the rate of increase in V_T as a function of \dot{V}_E may become blunted in the presence of critically-high inspiratory constraints (Guenette et al., 2013), we individually determined the V_T - \dot{V}_E inflection point using the V-slope method and modified Hey plots (Hey et al., 1966). These measurements were later verified by a second observer. Borg leg discomfort and dyspnea ratings (0-10 category-ratio scale)

were also obtained at each work rate. VR_{dyn} and dyspnea scores at the highest equivalent work rate across all groups (60 W) were compared to sex- and age-adjusted normative data, as established in our laboratory (Neder et al., 2020). Scores $>75^{\text{th}}$ centile indicate “*very severe*” dyspnea burden (Neder et al., 2020).

4.3.3 Statistical Analysis

Given multiple outcomes, we were unable to *a priori* power our study. Based on our previous investigations in *f*-ILD, however, a sample size of at least 18 patients with *f*-ILD in each category and 18 controls was deemed sufficient to detect the minimal clinically important difference of 1 Borg-unit in dyspnea at the highest equivalent work rate (60 W) achieved by all participants (Ries, 2005) $SD=1$, $\alpha=0.05$, and $\beta=0.80$). One-way ANOVA with post hoc Bonferroni test and χ^2 test (for categorical variables) assessed between-group differences in participant characteristics, resting lung function, and selected CPET variables. Two-way repeated measure ANOVA with Bonferroni post hoc multiple comparisons was used to evaluate the effect of group (fixed factor) on key dependent variables during incremental exercise (repeated factor). Statistical significance was set at $p<0.05$.

4.4 Results

4.4.1 General Characteristics and Resting Lung Function

Controls and patients were well-matched by demographic and anthropometric characteristics, though BMI was numerically higher in the *f*-ILD groups (Table 4). As expected, most patients had a smoking history (mostly cigarette). More patients in the $DL_{CO}<40\%$ predicted group reported “*severe*” dyspnea in daily life (mMRC score ≥ 3) compared to other groups. The $DL_{CO}<40\%$ predicted group showed the lowest spirometric values and “*static*” lung volumes; for instance, while ~ half of the $DL_{CO}\geq 40\%$ predicted group had mild restriction, 3 patients in the

DL_{CO}<40% predicted group showed moderate-to-severe decrements in TLC ($p<0.05$). Lower DL_{CO} in the latter group was associated with lower V_A and V_A/TLC ratio: as DL_{CO} decreased to a greater extent than V_A, these patients showed the lowest K_{CO} ($p<0.05$; Table 4).

4.4.2 Exercise Tolerance

Peak exercise capacity – either expressed as work rate or $\dot{V}O_2$ – was lower in the DL_{CO}<40% predicted group compared to other controls ($p<0.05$; Table 5 and Figure 9 A). For instance, the frequency of subjects showing peak work rate and/or peak $\dot{V}O_2 < LLN$ was two-fold greater in the DL_{CO}<40% predicted group compared to their counterparts with higher DL_{CO} (Table 5).

4.4.3 Metabolic and Cardiovascular Responses to Exercise

Despite no between-group differences in $\dot{V}O_2$ -work rate slope (typically between 9-11 mL/min/W in both groups) (Figure 9 A), $\dot{V}CO_2$ increased at a faster rate than $\dot{V}O_2$ at a lower work rate in the DL_{CO}<40% predicted group (Figure 9 B&C), i.e., higher respiratory exchange ratio (RER) at a given exercise intensity (Figure 9 D). This was also influenced by an earlier “anaerobic” threshold as a function of $\dot{V}O_2$ or work rate (Table 5). Given similar $\dot{V}O_2$ at a given exercise intensity (Figure 9 D) but a steeper heart rate- $\dot{V}O_2$ slope (Table 4), patients showed lower submaximal and peak O₂ pulse than controls, a finding particularly pronounced in those showing DL_{CO}<40% predicted (Table 5 and Figure 9 F). Interestingly, patients in the latter group showed a consistent upward inflection in heart rate close to peak exercise (Figure 9 E), resulting in a downward shift in O₂ pulse (Figure 9 F).

4.4.4 Ventilatory and Gas Exchange Responses to Exercise

Patients from the DL_{CO}<40% predicted group showed significantly higher \dot{V}_E at a given work rate (Figure 10 A) and metabolic demand $\dot{V}CO_2$ (Figure 10 B). Thus, $\dot{V}_E/\dot{V}CO_2$ was

consistently higher throughout exercise (Figure 10 C) and VR_{dyn} was lower (Figure 10 D) in these subjects compared to the other groups ($p<0.05$). In fact, a significantly higher fraction of patients showing $DL_{\text{CO}}<40\%$ predicted had moderate (≥ 34) and severe (≥ 40) increases in $\dot{V}_E/\dot{V}_{\text{CO}_2}$ and VR_{dyn} , below the sex- and age-adjusted lower limit of normal (J A Neder et al., 2022) at the highest equivalent work rate of 60 W ($p<0.05$; Table 5). These abnormalities were associated with lower P_{ETCO_2} and S_{pO_2} (Figure 10 E&F) throughout exercise in the former group ($p<0.05$).

4.4.5 Operating Lung Volumes and Breathing Pattern During Exercise

As expected by the restrictive abnormalities (Table 4), both patient groups showed a downward shift in the absolute operating lung volumes but higher EILV%TLC compared to controls (Figure 11 A-C & D-F, respectively $p<0.05$). The $DL_{\text{CO}}<40\%$ predicted group reached similar end-exercise EILV%TLC (Figure 11 D-F) at a significantly lower peak work rate (Table 5) compared to $DL_{\text{CO}}\geq 40\%$ predicted ($p<0.05$). Similar V_T (Figure 12 A) in the setting of an IC_{dyn} (~0.2-0.3 L lower in the $DL_{\text{CO}}<40\%$ predicted group compared to the $DL_{\text{CO}}\geq 40\%$ predicted group (Table 5)) implied a consistent trend to higher V_T/IC_{dyn} ratio throughout exercise in the $DL_{\text{CO}}<40\%$ predicted group (Figure 12 B). In fact, critically high inspiratory constraints (V_T/IC_{dyn} 70-80%) occurred at work rates ~10-15 W lower in this group (Table 5). In keeping with greater inspiratory constraints, a faster respiratory rate ($p<0.05$; Figure 12 C&D) was instrumental in explaining the higher \dot{V}_E shown by the $DL_{\text{CO}}<40\%$ predicted group (Figure 10 A-D). In association with a faster respiratory rate, both the inspiratory (T_I) and expiratory time (T_E) were significantly lower in the latter group (Figure 12 E&F): given similar T_I /total respiratory time (T_{TOT}) (Figure 12 G), the $DL_{\text{CO}}<40\%$ predicted group showed higher mean inspiratory flows (V_T/T_I) ($p<0.05$; Figure 12 H).

4.4.6 Sensory Responses to Exercise

Patients from the $DL_{CO}<40\%$ predicted group reported the highest leg discomfort scores during submaximal exercise (Figure 9 G&H), a finding particularly noticeable at higher exercise intensities. For instance, a threefold lower change in work rate in the $DL_{CO}<40\%$ predicted group (60-70W) compared to the $DL_{CO}\geq 40\%$ predicted group (60-90W) led to the same increase in mean leg discomfort scores (“3” to “5”) (Figure 9 G). Given a leftward shift in the submaximal dyspnea-work rate relationship (Figure 13 A), the $DL_{CO}<40\%$ predicted group showed significantly steeper dyspnea-work rate and dyspnea- $\dot{V}O_2$ slopes compared to their counterparts and controls ($p<0.05$; Table 5). Moreover, a higher fraction of patients in the $DL_{CO}<40\%$ predicted group reported dyspnea scores in the “very severe” range when compared to normative data (Neder et al., 2020) ($p<0.05$; Table 5). In contrast, the dyspnea- \dot{V}_E relationship did not differ between the two *f*-ILD groups ($p<0.05$; Table 5 and Figure 13 B). Interestingly, the between group dyspnea scores, as exercise progressed, were reduced versus decreasing ventilatory reserves (VR_{dyn} ; Figure 13 C), and lowering inspiratory reserves (IRV/TLC; Figure 13 D).

4.5 Discussion

The current study shed novel light into the physiological and sensory mechanisms by which a severely reduced single-breath DL_{CO} (<40% predicted) is associated with more pronounced impairment in exercise tolerance in patients showing the common phenotype of *f*-ILD (Cottin et al., 2018; Cottin et al., 2019). As we *a priori* postulated, such a severe decrement in gas transfer marked interconnected abnormalities in cardiocirculatory (tachycardia relative to $\dot{V}O_2$), metabolic (earlier shift to anaerobic metabolism), ventilatory (excess ventilation), mechanical (inspiratory constraints) and pulmonary gas exchange (hypoxemia and hyperventilation) responses to exercise which were translated into a higher burden of respiratory breathlessness and peripheral leg

discomfort symptoms. In association with our previous results showing the clinical relevance of a low DL_{CO} in the initial stages of *f*-ILD (Faisal et al., 2016; Smyth et al., 2023b), these data expose the key role of DL_{CO} as a physiological biomarker of exercise intolerance across the spectrum of disease severity.

*4.5.1 Resting Functional Abnormalities According to the Severity of DL_{CO} Impairment in *f*-ILD*

The $DL_{CO}<40\%$ predicted group showed significantly lower spirometric values and more relevant restrictive abnormalities compared to their counterparts with higher DL_{CO} (Table 4). Statistically lower VC and numerically lower IC, in particular, were secondary to greater decrements in TLC than residual volume and functional residual capacity, respectively. Thus, patients from the $DL_{CO}<40\%$ predicted group started exercising with less “room” for V_T expansion (Guenette et al., 2013), a finding that strongly contributes to exertional dyspnea in these patients (*also see Inspiratory Constraints on Exertion and a Severely Reduced DL_{CO} in *f*-ILD*) (Faisal et al., 2016). Lower resting lung volumes also imply that part of the severe impairment in DL_{CO} can be ascribed to lower distribution volume, i.e., V_A (Table 4). Interestingly, a lower V_A/TLC ratio indicates a greater degree of ventilation distribution abnormalities (Kaminsky et al., 2007), further reducing DL_{CO} (Hughes, 2003). Out-of-proportion decreases in DL_{CO} relative to volume loss (i.e., lower K_{CO}) points to impaired gas exchange efficiency and likely pulmonary vascular abnormalities (Panagiotou et al., 2016), leading to a high \dot{V}_E/\dot{V}_{CO_2} (J. A. Neder et al., 2022b) (*also see Excess Exertional Ventilation and a Severely Reduced DL_{CO} in *f*-ILD*). Jointly, therefore, lower lung volumes, thickened alveolar-capillary membrane in more severe patients, disturbed pulmonary blood flow (Keogh & Crystal, 1980), and ventilation distribution inhomogeneities resulting in \dot{V}_A/\dot{Q}_c mismatch may have contributed to the markedly slow rate of CO transfer in the $DL_{CO}<40\%$ predicted group.

4.5.2 Excess Exertional Ventilation and a Severely Reduced DL_{CO} in *f*-ILD

Excess ventilation has been described in a plethora of cardiopulmonary diseases in which breathlessness and exercise intolerance are dominant features (Dempsey et al., 2022; Neder, 2020; J. A. Neder et al., 2022b). Both inefficient ventilation (i.e., increased “wasted” ventilation in areas of V_D) (Robertson, 2015) and alveolar hyperventilation (manifested as low P_aCO_2) (Whipp, 2008) may explain a high \dot{V}_E/\dot{V}_{CO_2} in these patients (Neder, 2020; Robertson, 2015). In the current study, excess ventilation, even at rest, was a noticeable abnormality in the DL_{CO}<40% predicted group (Figure 10 C). As mentioned, DL_{CO} is influenced by \dot{V}_A/\dot{Q}_c mismatch (Petersson & Glenny, 2014), particularly the extension of areas of high \dot{V}_A/\dot{Q}_c , i.e., dead space “effect” (Robertson, 2015). Areas of low \dot{V}_A/\dot{Q}_c (“shunt effect”), a key determinant of hypoxemia in *f*-ILD (Agustí et al., 1991), also contribute to decreasing DL_{CO} and increasing Bohr-Enghoff’s V_D (Robertson, 2015). Fibrotic tissue deposition, architectural distortion, increased axial airway traction, patchy foci of enlarged airspaces, and vascular obliteration/dysfunction (Keogh & Crystal, 1980), common to all *f*-ILDs (Cottin et al., 2018; Cottin et al., 2019), may provide the structural substrate to \dot{V}_A/\dot{Q}_c disturbances, high V_D , and low P_aO_2 , which contribute to the high \dot{V}_E/\dot{V}_{CO_2} shown by the DL_{CO}<40% predicted group (Table 5 and Figure 10 D) (J. A. Neder et al., 2022a).

It should be recognized, however, that the DL_{CO}<40% predicted group showed higher RER since the earlier stages of exercise (Figure 9 D) (i.e., hyperventilation) well before any compensatory influence of respiratory alkalosis or metabolic acidosis. Although we did not measure the source of carotid chemostimulation on hypoxia (a low P_aO_2) (Dempsey et al., 2022), S_pO_2 was only mildly reduced at these low exercise intensities (i.e., $\geq 90\%$) (Figure 10 F). Thus, other sources of ventilatory (over)stimulation likely contributed to a high \dot{V}_E/\dot{V}_{CO_2} in the DL_{CO}<40% predicted group (e.g., increased central chemosensitivity (low CO_2 “set-point”),

airway-lung-chest wall mechano-(vagal) receptors overactivity, (Mendonca et al., 2014; Van Meerhaeghe et al., 1981), heightened ergoreceptor discharge (Dempsey et al., 2022) (*also see Heightened Leg Discomfort on Exertion and a Severely Reduced DL_{CO} in f-ILD*), and increased pulmonary vascular pressures (Dempsey, 2019). It is also noteworthy that a high V_D frequently coexists with a low P_aCO₂, exposing the challenges faced by the central controller to stabilize “mean” alveolar PCO₂ when the ventilatory output is not readily translated into the expected increase in alveolar ventilation (Neder, 2020; Whipp, 2008). In any case, the lowest (Figure 10 E) and blunted (lower rest-peak difference in Table 5) P_{ET}CO₂ in the DL_{CO}<40% predicted group may have resulted from expired PCO₂ dilution due to enlarged V_D /impaired perfusion plus alveolar hyperventilation (Robertson, 2015).

4.5.3 Inspiratory Constraints on Exertion and a Severely Reduced DL_{CO} in f-ILD

In keeping with resting lung function data indicating slightly lower lung volumes (Table 4), patients from the DL_{CO}<40% predicted group reached similar V_T/IC_{dyn} and EILV/TLC at significantly lower peak work rates compared to DL_{CO}≥40% predicted (Table 5). Of note, the V_T inflection point, indicating critical constraints to further lung-chest wall displacement (Guenette et al., 2013), occurred at similar \dot{V}_E in both patient groups (~45 L/min; Figure 10 A) (*also see Exertional Dyspnea and a Severely Reduced DL_{CO} in f-ILD*). Given the higher ventilatory response (Figure 10 A-D), however, this occurred at significantly lower exercise intensities. In the setting of higher operating lung volumes and a closer proximity to TLC (Figure 11 D-F) (Dempsey et al., 2022), the heightened ventilatory requirement in this group were primarily met by faster respiratory rates rather than larger V_{TS} (Figure 12 C-D). Tachypnea may have also been influenced by higher chemostimulation when S_pO₂ decreased to 88% or lower, i.e., values that are more likely to be associated with substantial carotid body stimulation (PaO₂<60 mmHg) (Du Plessis et al.,

2018). Regardless of the underlying mechanisms, a faster breathing frequency at a similar duty cycle (Figure 12 G) implies a shorter T_I (Figure 12 F); consequently, the mean inspiratory flow (V_T/T_I ratio) was higher in the $DL_{CO}<40\%$ predicted group (Figure 12 H). As long postulated by Burdon and colleagues (Burdon et al., 1983), shorter T_I and higher V_T/T_I may serve to optimize V_T and breathing frequency, likely minimizing the elastic and resistive work of breathing and, potentially, breathlessness in *f*-ILD.

4.5.4 Heightened Leg Discomfort on Exertion and a Severely Impaired DL_{CO} in *f*-ILD

There is growing evidence that decrements in DL_{CO} are associated with abnormalities in peripheral (and potentially respiratory) muscle structure and function in *f*-ILD (Molgat-Seon et al., 2021; Panagiotou et al., 2016). A higher sense of leg discomfort throughout exercise in the $DL_{CO}<40\%$ predicted group (Figure 9 G&H) is likely multifactorial. For instance, these patients reported more severe dyspnea in daily life (Table 4); thus, they were likely less active and more deconditioned. Lower O_2 delivery secondary to reduced arterial O_2 content likely contributed, as well as any impairment in intra-muscular blood flow distribution (Marillier et al., 2023a). Whether the consistent downward shift in O_2 pulse closer to exercise cessation (Figure 9 F) signals impaired stroke volume (secondary to higher pulmonary vascular pressures) (Degani-Costa et al., 2015) and/or the consequences of more severe hypoxemia (reflex increase in heart rate and/or reduced arterial-venous O_2 gradient) remain unclear, demanding invasive CPET. We recently showed that reduced convective O_2 delivery (Marillier et al., 2023a), either secondary to hypoxemia and/or lower muscle blood flow, is mechanistically linked to heightened neuromuscular (contractile) fatigue (Marillier et al., 2021b) and perceived sense of fatigability (Marillier et al., 2023b), both being predictors of poor exercise tolerance in *f*-ILD. As shown in Table 5, patients from the $DL_{CO}<40\%$ predicted group did present with an earlier “anaerobic” threshold which may have

further increased the discharge of over-excited ergoreceptors (Dempsey et al., 2022). It is interesting to note the temporal concomitance between an upward shift in leg discomfort with the V_T inflection point (triangles in [Figure 9 G&H](#)). Although this may not reflect causality, putative explanations include: *a*) given the parallel acceleration of dyspnea at this point ([Figure 13](#)), the patients may have become more aware of any simultaneous uncomfortable sensations; *b*) negative hemodynamic consequences of heightened pleural pressure swings and/or blood flow redistribution to the overloaded respiratory muscles (Dempsey et al., 2022) may have further impaired muscle O_2 delivery, and *c*) the blunting effect of the respiratory compensation to lactic acidosis on V_T with simultaneous increase in breathing frequency (Neder & Stein, 2006).

*4.5.5 Exertional Dyspnea and a Severely Impaired DL_{CO} in *f*-ILD*

A noticeable finding of the present study was the similar peak dyspnea scores reported by patients and controls. Given ~45% (versus controls) and ~20% (versus $DL_{CO} \geq 40\%$ predicted) lower peak work rate in the $DL_{CO} < 40\%$ predicted group, dyspnea increased at a faster rate in the latter group ([Table 5](#) and [Figure 13 A](#)). We, therefore, confirmed a recurrent finding across our studies involving patients with obstructive [e.g., chronic obstructive pulmonary disease (COPD), cystic fibrosis (Neder et al., 2019a)] and restrictive (ILD) (Faisal et al., 2016) abnormalities: the close relationship between metrics of demand-capacity imbalance and exertional dyspnea. For instance, differences in dyspnea intensity between patients and controls were markedly lessened (versus VR_{dyn}) or disappeared (versus IRV/TLC) when the symptom was related to metrics of reduced ventilatory and volume reserves, respectively ([Figure 13 C&D](#)). This is consistent with the notion that increased dyspnea in *f*-ILD largely reflects the heightened awareness of increased neural respiratory drive (Mendonca et al., 2014) triggered by alterations in pulmonary gas exchange efficiency (reducing VR_{dyn}) and respiratory mechanics (decreasing IRV/TLC)

(Schaeffer et al., 2018). In keeping with our recent results in COPD (Berton et al., 2023), [Figure 10 D](#) illustrates the advantages of submaximal VR_{dyn} to expose the seeds of exertional dyspnea since peak VR (the traditional approach to suggest ventilatory limitation) did not differ between patients and controls. Of note, patients showing $DL_{CO}<40\%$ predicted were more likely to report dyspnea scores within the “*very severe*” range ([Table 5](#)), a cut-off that consistently pointed to higher \dot{V}_E/\dot{V}_{CO_2} , greater inspiratory constraints, and poorer exercise tolerance in COPD (Neder et al., 2020). The differences in dyspnea *trajectory* as the ventilatory and volume reserves diminished with exercise progression were also informative. Thus, dyspnea rose linearly as VR_{dyn} decreased without a discernible “*breakpoint*” ([Figure 13 C](#)); conversely, it quickly accelerated when the volume reserve to further inspiration reached excessively low values (~15% from TLC at ~45 L/min \dot{V}_E in both patient groups) ([Figure 13 D](#)) (Guenette et al., 2013). It follows that to avoid the emergence of intolerable dyspnea, *f*-ILD patients might benefit from training modalities that are not associated with sustained increases in \dot{V}_E above a certain “*critical*” level.

4.5.6 Study Weaknesses and Strengths

Our results are largely descriptive, and we carefully avoided suggesting any cause-effect relationship between $DL_{CO}<40\%$ predicted and the associated resting and exercise outcomes. Thus, we emphasized that $DL_{CO}<40\%$ predicted signals (i.e., predicts) multiple abnormal responses to exertion, which are beyond its most logical correlate: hypoxemia. In this context, they provide strong support for the contentions by Enright about the relevance of DL_{CO} in helping clinical-decision making in pulmonology (Enright, 2016). Although we did not measure mouth pressure during the DL_{CO} maneuvers, Kaminsky and Jarzembosky reported that variations were not associated with the measured DL_{CO} value in a real-life study which included ILD patients (Kaminsky & Jarzembowski, 2019). We opted for the % predicted criterion to define a severely

impaired DL_{CO} since z-scores-based classifications have not yet been extensively validated. To improve the external validity of our results, we did not exclude patients with a previous smoking history. Importantly, however, emphysema extension was defined as only “*mild*” (Wille et al., 2016) by trained radiologists in all patients. In particular, no patient with CPFE or resting pulmonary hypertension were included (Degani-Costa et al., 2015), decreasing sample heterogeneity. Both *f*-ILD groups showed a numerically, but not statistically, higher BMI than controls (though typically in the mild obesity range), and increased mass displacement is known to worsen dyspnea; thus, additional studies are required to investigate whether dyspnea further increases when moderate-to-severe obesity and DL_{CO}<40% predicted coexist. Although the relative contribution of lung mechanical versus gas exchange mechanisms of breathlessness vary as *f*-ILD etiologies progress (Keogh & Crystal, 1980), this seems a less relevant shortcoming in a transversal study. Cycling is associated with less hypoxemia compared to walking (Du Plessis et al., 2018); consequently, we may have underestimated the severity of arterial O₂ desaturation in daily life. Nevertheless, less exercise-induced hypoxemia gave us the opportunity to investigate the integrated physiological response to exercise and their sensory consequences without the overruling influence of a markedly increased hypoxic drive (Du Plessis et al., 2018). Also, from a positive perspective, only a minority of our patients were under long-term O₂ therapy (n=11), reducing the potential confounding effects of acute O₂ supplementation withdrawal (for CPET performance) on exertional dyspnea. We restrained our analysis to dyspnea intensity, and it remains unknown whether dyspnea descriptors (O'Donnell et al., 1998; Schaeffer et al., 2019) would change in those with a severely reduced DL_{CO}. Since severe hypoxemia may compromise cerebral oxygenation on exertion in *f*-ILD (Marillier et al., 2021a), it remains unclear whether

“*central*” fatigue (Marillier et al., 2021c) may contribute to poorer exercise tolerance in the $DL_{CO}<40\%$ predicted group.

4.6 Conclusion

A severely reduced single-breath DL_{CO} ($<40\%$) marks poor exercise tolerance in patients with *f*-ILD due to multiple interconnected mechanisms (disturbed hemodynamics, a precocious shift to skeletal muscle anaerobic metabolism, excess exertional ventilation secondary to heightened afferent stimuli including hypoxemia, critically high inspiratory constraints) which ultimately led to intolerable respiratory (dyspnea) and peripheral (leg discomfort) symptoms. Given the close association between impaired physical performance and symptom burden with morbidity and poor health-related quality of life in *f*-ILD (Chang et al., 1999; Holland, 2010; Swigris et al., 2018), this sub-set of patients might derive particular benefit from interventions to lessen the ventilatory requirements (walking aids, exertional O_2 supplementation (Molgat-Seon et al., 2019)), treatment of cardiovascular comorbidities known to increase afferent stimuli (J. A. Neder et al., 2022b), exercise reconditioning (Holland, 2010), volume constraints (anti-fibrotic therapy as indicated (McCarthy & Keane, 2022)), weight loss in obesity, and, in selected patients, dyspnea perception (low dose opiates (Milne et al., 2020b)).

Table 4. Selected participant characteristics and resting lung function in controls and *f*-ILD patients separated by the severity of DL_{CO} impairment. (Chapter 4)

Variables	Patients (n=67)			p-value
	Controls (n=22)	DL _{CO} ≥40% (n=43)	DL _{CO} <40% (n=24)	
General characteristics				
Sex, % male	64	74	71	0.655
Age, years	72 ± 6	71 ± 8	67 ± 14	0.308
Height, cm	170.1 ± 7.7	171.1 ± 8.1	170.3 ± 9.0	0.874
Mass, kg	79.1 ± 13.0	86.9 ± 15.3	86.4 ± 17.6	0.145
BMI, kg/m ²	27.2 ± 3.3	29.6 ± 4.1	29.6 ± 4.6	0.072
Smoking, pack-years	2 ± 7	19 ± 16 *	21 ± 20 *	<0.001
mMRC				
Median (range)	0 (0-1)	2 (0-4)	2 (1-4)	<0.001
≥2, n (%)	0 (0)	25 (58) *	16 (67) *	<0.001
≥3, n (%)	0 (0)	9 (21) *	9 (38) *†	0.006
Lung function				
FEV ₁ , % predicted	98.4 ± 17.5	81.9 ± 15.4 *	69.5 ± 13.6 *†	<0.001
FVC, % predicted	108.1 ± 14.9	82.9 ± 16.6 *	71.2 ± 17.0 *†	<0.001
VC, % predicted	105.8 ± 12.8	80.3 ± 16.2 *	96.5 ± 17.1 *†	<0.001
FEV ₁ /FVC %	69 ± 8	76 ± 6 *	77 ± 10 *	0.005
TLC				
% predicted	96.7 ± 9.1	70.8 ± 13.2 *	63.3 ± 13.8 *	<0.001
≥ 70% predicted, n (%)	22 (100)	22 (51) *	6 (25) *†	<0.001
≥ LLN, n (%)	22 (100)	9 (21) *	2 (8) *	<0.001
IC, % predicted	114.7 ± 20.0	79.1 ± 15.1	68.0 ± 20.2	<0.001
FRC, % predicted	83.3 ± 17.4	65.9 ± 17.1 *	61.0 ± 14.4 *	<0.001
RV, % predicted	82.8 ± 20.8	57.8 ± 19.0 *	55.1 ± 18.7 *	<0.001
FRC/TLC, %	47 ± 9	50 ± 7	52 ± 7	0.149
RV/TLC, %	32 ± 8	29 ± 6	31 ± 7	0.275
DL _{CO} , % predicted	86.3 ± 16.8	53.3 ± 11.7 *	32.4 ± 4.7 *†	<0.001
V _A , % predicted	90.4 ± 11.9	67.1 ± 13.3 *	54.1 ± 15.7 *†	<0.001
K _{CO} , % predicted	96.2 ± 19.7	80.3 ± 14.4 *	64.8 ± 19.0	<0.001
V _A /TLC, %	85 ± 10	86 ± 10	78 ± 16 †	0.028
MVV _{est} , L/min	94.0 ± 24.0	80.7 ± 16.3	70.0 ± 16.8	<0.001

Unless otherwise indicated, data are mean ± standard deviation or (frequency). *p*-values are for main effect according to one-way ANOVA or two-sided significance from χ^2 test. Significant Bonferroni adjusted *post hoc* between-group multiple comparisons are indicated by: * *p*<0.05 vs. controls; † *p*<0.05 vs. DL_{CO}≥40% predicted. *Definition of abbreviations:* DL_{CO}: diffusion capacity of the lung for carbon monoxide; mMRC: modified Medical Research Council; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; VC: vital capacity; TLC: total lung capacity; LLN: lower limit of normal; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume; V_A: alveolar volume; K_{CO}: transfer coefficient; MVV_{est}: estimated (from FEV₁) maximal voluntary ventilation.

Table 5. Selected peak and submaximal physiological and sensory responses to incremental CPET in controls and *f*-ILD patients separated by the severity of DLCO impairment. (*Chapter 4*)

Variables	Patients (n=67)			p-value
	Controls (n=22)	DLCO \geq 40% (n=43)	DLCO<40% (n=24)	
Power				
Work Rate				
W	136 \pm 37	93 \pm 25 *	74 \pm 22 * \dagger	<0.001
% predicted	117.2 \pm 26.5	75.0 \pm 19.5 *	57.2 \pm 15.3 * \dagger	<0.001
<LLN, n (%)	0 (0)	14 (33) *	16 (67) * \dagger	<0.001
Metabolic/cardiovascular				
$\dot{V}O_2$				
L/min	2.02 \pm 0.61	1.50 \pm 0.44 *	1.18 \pm 0.33 * \dagger	<0.001
% predicted	109.0 \pm 22.7	75.1 \pm 18.6 *	57.9 \pm 12.7 * \dagger	<0.001
<LLN, n (%)	1 (5)	19 (44) *	18 (75) * \dagger	<0.001
$\dot{V}O_2$ at the estimated LT				
$\dot{V}O_2$, L/min	1.28 \pm 0.31	1.05 \pm 0.29 *	0.84 \pm 0.23 * \dagger	<0.001
$\dot{V}O_2$, % predicted $\dot{V}O_{2\max}$	59.9 \pm 12.6	52.2 \pm 11.3 *	41.8 \pm 9.7 * \dagger	<0.001
W	76.6 \pm 21.8	50.5 \pm 17.3 *	38.9 \pm 20.4 * \dagger	<0.001
RER	1.14 \pm 0.08	1.14 \pm 0.12	1.19 \pm 0.12	0.0157
Heart Rate, beats/min	138 \pm 22	127 \pm 21	121 \pm 22 *	0.046
O ₂ pulse, ml/beat	14.8 \pm 3.9	11.9 \pm 2.9 *	9.8 \pm 2.3 * \dagger	<0.001
Heart Rate- $\dot{V}O_2$ slope, beat/L	43 \pm 15	39 \pm 16	55 \pm 25 \dagger	0.004
Ventilatory/gas exchange				
\dot{V}_E				
L/min	74.8 \pm 24.5	63.0 \pm 17.1	61.3 \pm 15.4	0.033
At 60 W, L/min	30.8 \pm 4.0	40.5 \pm 7.6 *	47.9 \pm 9.4 * \dagger	<0.001
VR, %	21.4 \pm 14.9	23.7 \pm 17.4	13.7 \pm 13.4 \dagger	0.052
VR _{dyn} , at 60W				
%	64.9 \pm 10.0	46.5 \pm 15.0 *	31.7 \pm 11.5 * \dagger	<0.001
<LLN, N (%)	1 (5)	15 (39) *	17 (70) * \dagger	<0.001
$\dot{V}_E/\dot{V}CO_2$	32.7 \pm 3.1	37.6 \pm 5.6 *	45.2 \pm 9.3 * \dagger	<0.001
$\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$				
L/min/L/min	28.8 \pm 2.1	35.4 \pm 4.6 *	42.1 \pm 8.4 * \dagger	<0.001
\geq 34, n (%)	0 (0)	26 (60) *	22 (92) * \dagger	<0.001
\geq 40, n (%)	0 (0)	7 (16) *	11 (46) * \dagger	<0.001
$\dot{V}_E/\dot{V}CO_2$ at 60W	30.4 \pm 2.1	36.1 \pm 4.1 *	41.0 \pm 5.8 * \dagger	<0.001
P _{ET} CO ₂				
mmHg	34.5 \pm 3.4	32.8 \pm 4.2 *	28.5 \pm 4.8 * \dagger	<0.001
Δ Rest-Peak, mmHg	-5.6 \pm 2.0	-3.0 \pm 2.0 *	-1.1 \pm 1.2 * \dagger	<0.001
At $\dot{V}_E/\dot{V}CO_{2\text{ nadir}}$, mmHg	39.5 \pm 2.7	35.4 \pm 4.0 *	31.2 \pm 4.3 * \dagger	<0.001
At 60W, mmHg	38.5 \pm 2.8	35.0 \pm 3.9 *	31.2 \pm 4.8 * \dagger	<0.001
S _p O ₂				
%	94.0 \pm 5.5	89.7 \pm 6.0 *	87.2 \pm 5.9 *	<0.001
<90%, n (%)	4 (18)	19 (44) *	13 (54) *	0.036
<88%, n (%)	2 (9)	11 (26) *	11 (46) * \dagger	0.020

Δ Peak-Rest, %	3.3 ± 5.6	6.3 ± 5.3	7.4 ± 4.2 *	0.026
At 60W, %	96.9 ± 1.5	92.5 ± 4.5 *	89.6 ± 4.4 *†	<0.001
Operating lung volumes/breathing pattern				
V _T , L	2.14 ± 0.62	1.66 ± 0.38 *	1.45 ± 0.36 *	<0.001
f _B , breaths/min	35 ± 6	39 ± 9	43 ± 8 *	0.008
f _B /V _T , breath/min/L	18.2 ± 6.8	25.1 ± 9.5 *	32.4 ± 12.8 *†	<0.001
IC _{dyn} , L	3.04 ± 0.77	2.14 ± 0.51*	1.88 ± 0.44*	<0.001
Δ IC _{dyn} Peak-Rest, L	0.04 ± 0.45	-0.01 ± 0.27	-0.01 ± 0.25	0.804
V _T /IC _{dyn}				
%	70.8 ± 11.7	79.5 ± 14.3 *	78.8 ± 9.1	0.031
%/peak work rate	0.55 ± 0.12	0.89 ± 0.24 *	1.20 ± 0.62 *†	<0.001
EILV/TLC				
%	84.7 ± 7.2	89.8 ± 7.8 *	89.3 ± 4.9	0.024
%/peak work rate	0.66 ± 0.14	1.02 ± 0.26 *	1.35 ± 0.59 *†	<0.001
Sensory				
Dyspnea				
Borg units	5.0 ± 2.6	5.3 ± 2.1	5.5 ± 2.4	0.819
Borg units-work rate slope	0.04 ± 0.02	0.05 ± 0.02	0.07 ± 0.04 *†	<0.001
Borg units/peak work rate	0.04 ± 0.02	0.06 ± 0.03	0.08 ± 0.05 *†	<0.001
Borg units/ $\dot{V}O_2$ slope	2.95 ± 1.63	4.03 ± 2.05	5.70 ± 3.24 *†	0.001
Borg units- \dot{V}_E slope	0.09 ± 0.05	0.11 ± 0.06	0.11 ± 0.06	0.264
>75 th centile at 60 W, n (%)	0 (0)	12 (28) *	9 (39) *†	0.005
Leg discomfort				
Borg units	5.6 ± 2.7	5.1 ± 2.1	5.1 ± 2.5	0.638
Borg units-work rate slope	0.04 ± 0.02	0.06 ± 0.03	0.07 ± 0.04 *	0.006
Borg units/peak work rate	0.04 ± 0.02	0.06 ± 0.03	0.08 ± 0.04 *	0.003
Borg units- $\dot{V}O_2$ slope	3.33 ± 1.56	4.33 ± 2.40	5.80 ± 3.39 *	0.006

Unless otherwise indicated, data are mean ± standard deviation or (frequency) at peak exercise. *p*-values are for main effect according to one-way ANOVA or two-sided significance from χ^2 test. Significant Bonferroni adjusted *post hoc* between-group multiple comparisons are indicated by: * *p*<0.05 vs. controls; † *p*<0.05 vs. DLCO_≥40% predicted. *Definition of abbreviations:* LLN: lower limit of normal; RER: respiratory exchange ratio; $\dot{V}O_2$: oxygen uptake; LT: estimated lactate threshold; \dot{V}_E : expired minute ventilation; VR: ventilatory reserve; VR_{dyn}: dynamic ventilatory reserve; $\dot{V}CO_2$: carbon dioxide output; P_{ET}CO₂: end-tidal partial pressure of carbon dioxide; S_pO₂: oxygen saturation by pulse oximetry; V_T: tidal volume; f_B: breathing frequency; IC_{dyn}: dynamic inspiratory capacity; EILV: end-expiratory lung volume; TLC: total lung capacity.

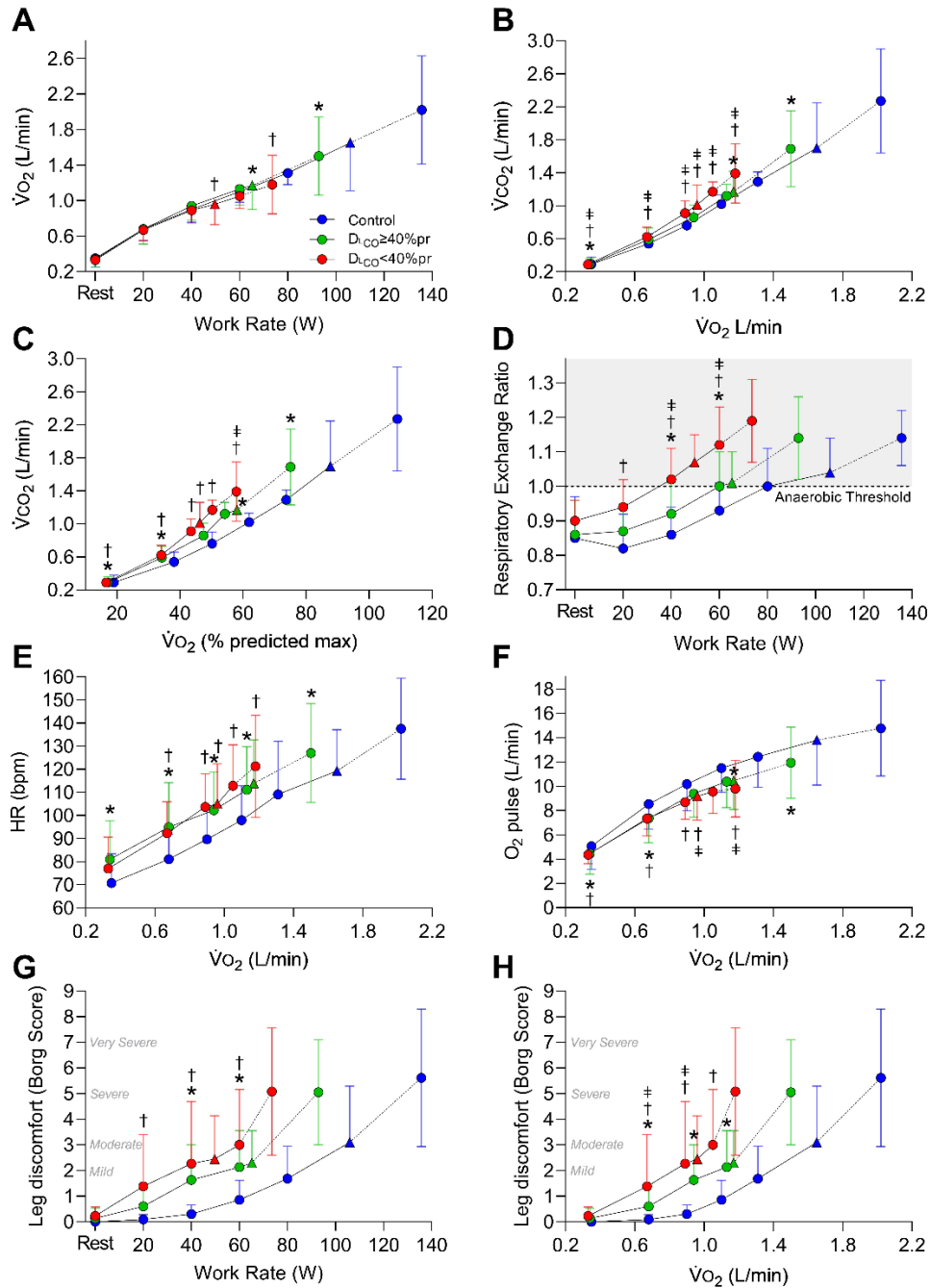


Figure 9. Metabolic, cardiovascular, and sensory responses to incremental exercise. (*Chapter 4*)

Metabolic (A-D), cardiovascular (E-F), and sensory (Borg leg discomfort; G-H) responses to incremental exercise in *f*-ILD patients with or without a severely decreased DLCO (*red and green circles*, respectively) and sex- and age-matched healthy controls (*blue circles*). *Triangles* are values at the tidal volume inflection point, reflecting critically high inspiratory constraints. Data are mean \pm standard deviation. *p*-values are for main-effect according to two-way ANOVA for repeated measures. Significant ($p < 0.05$) Bonferroni adjusted post hoc between-group comparisons are indicated by: *: DLCO $\geq 40\%$ predicted vs. controls; †: DLCO $< 40\%$ predicted vs. controls; ‡: DLCO $< 40\%$ predicted vs. DLCO $\geq 40\%$ predicted. *Definition of abbreviations:* $\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide output; RER: respiratory exchange ratio; HR: heart rate.

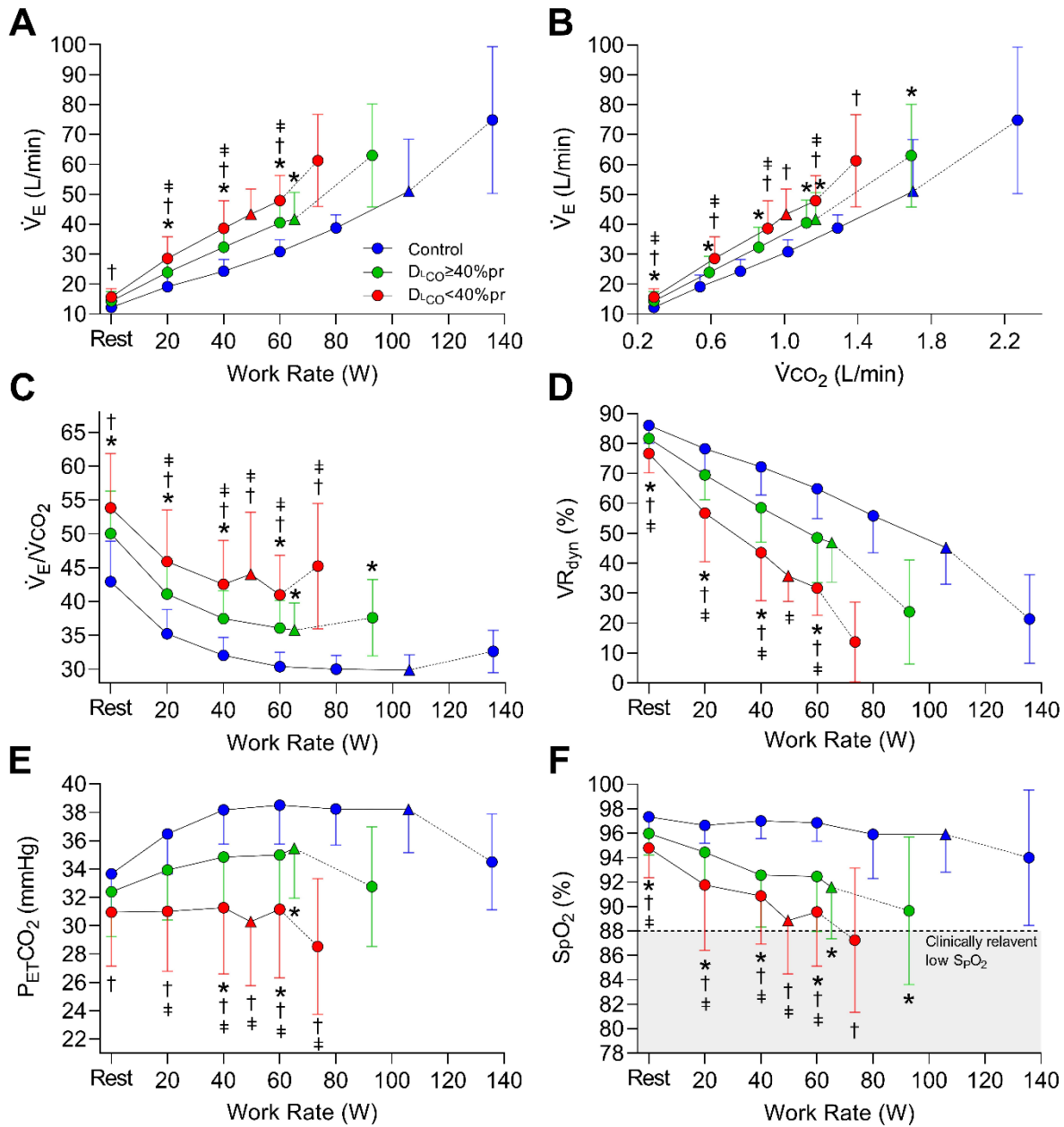


Figure 10. Ventilatory and gas exchange responses to incremental exercise. (*Chapter 4*)

Ventilatory (**A-B & D**) and gas exchange (**C & E-F**), responses to incremental exercise in *f*-ILD patients with or without a severely decreased DL_{CO} (*red and green circles*, respectively) and sex- and age-matched healthy controls (*blue circles*). *Triangles* are values at the tidal volume inflection point, reflecting critically high inspiratory constraints. Data are mean ± standard deviation. *p*-values are for main-effect according to two-way ANOVA for repeated measures. Significant (*p*<0.05) Bonferroni adjusted post hoc between-group comparisons are indicated by: *: DL_{CO}≥40% predicted vs. controls; †: DL_{CO}<40% predicted vs. controls; ‡: DL_{CO}<40% predicted vs. DL_{CO}≥40% predicted. *Definition of abbreviations*: \dot{V}_E : expired minute ventilation; \dot{V}_{CO_2} : carbon dioxide output; VR_{dyn} : dynamic ventilatory reserve; $P_{ET}CO_2$: end-tidal partial pressure for carbon dioxide; S_pO_2 : oxygen saturation by pulse oximetry.

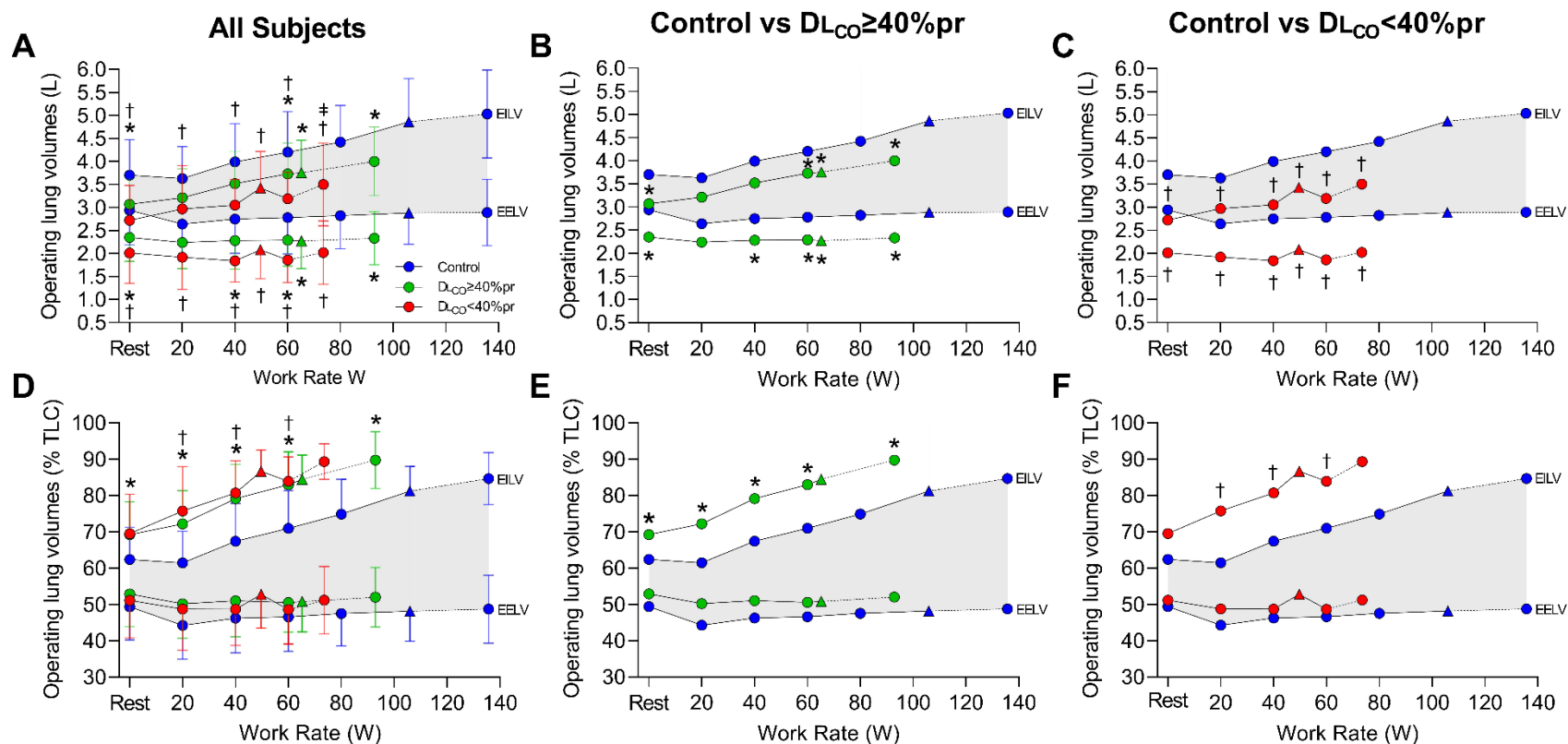


Figure 11. Operating lung volumes during incremental exercise. (Chapter 4)

Absolute (A-C) and relative to total lung capacity (TLC) (D-F) operating lung volumes during incremental exercise in *f*-ILD patients with or without a severely decreased DL_{CO} (red and green circles, respectively) and sex- and age-matched healthy controls (blue circles). Triangles are values at the tidal volume inflection point, reflecting critically high inspiratory constraints. Data are mean ± standard deviation. *p*-values are for main-effect according to two-way ANOVA for repeated measures. Significant (*p*<0.05) Bonferroni adjusted post hoc between-group comparisons are indicated by: *: DL_{CO} ≥ 40% predicted vs. controls; †: DL_{CO} < 40% predicted vs. controls; ‡: DL_{CO} < 40% predicted vs. DL_{CO} ≥ 40% predicted.

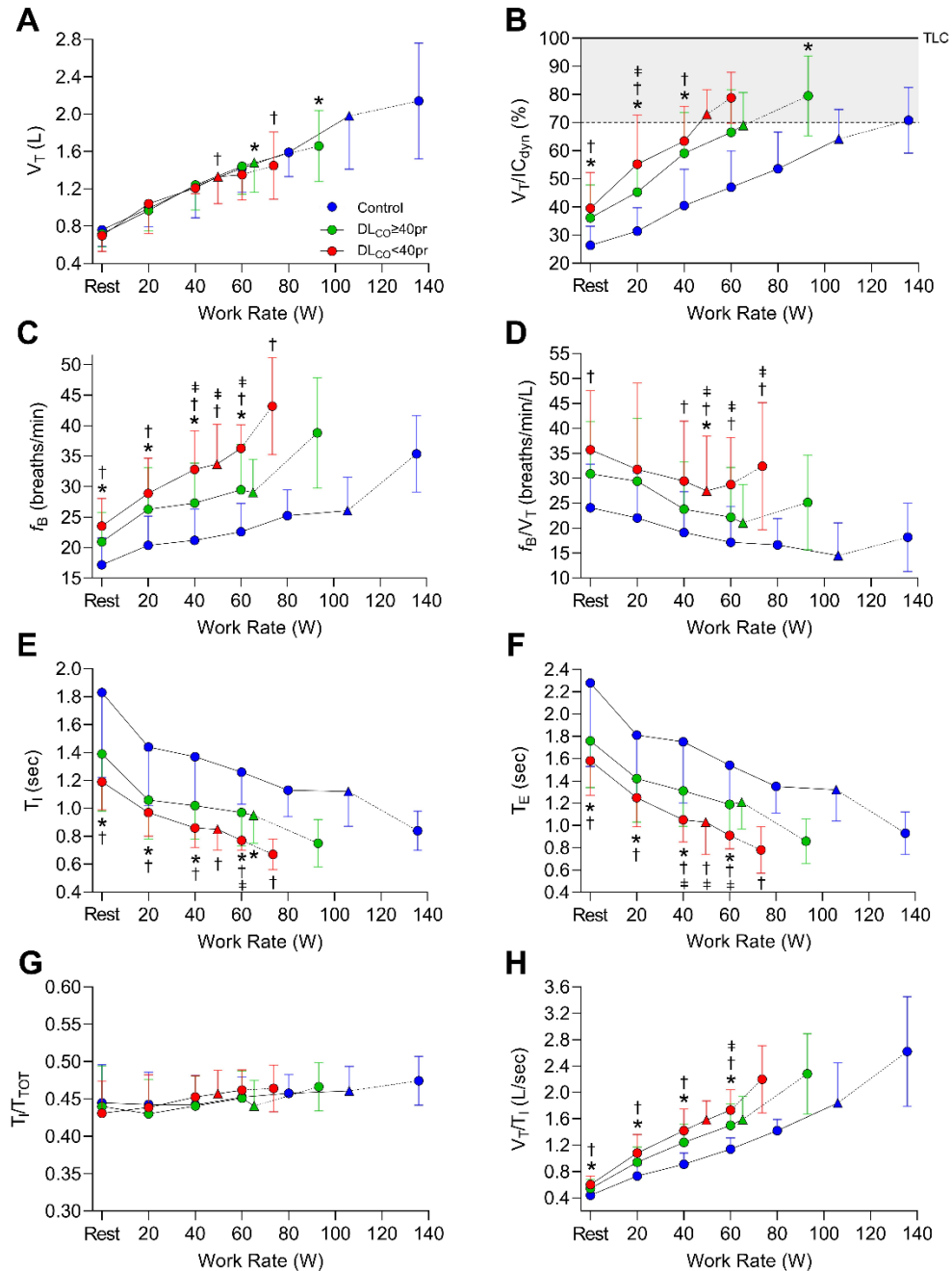


Figure 12. Breathing pattern and timing during incremental exercise. (*Chapter 4*)

Pattern (A-D) and timing (E-H) of breathing in response to incremental exercise in *f*-ILD patients with or without a severely decreased DLCO (*red* and *green circles*, respectively) and sex- and age-matched healthy controls (*blue circles*). *Triangles* are values at the tidal volume (V_T) inflection point, reflecting critically high inspiratory constraints. Data are mean \pm standard deviation. *p*-values are for main-effect according to two-way ANOVA for repeated measures. Significant ($p < 0.05$) Bonferroni adjusted post hoc between-group comparisons are indicated by: *: DLCO $\geq 40\%$ predicted vs. controls; †: DLCO $< 40\%$ predicted vs. controls; ‡: DLCO $< 40\%$ predicted vs. DLCO $\geq 40\%$ predicted. *Definition of abbreviations*: f_B : breathing frequency; IC_{dyn} : dynamic inspiratory capacity; T_I : inspiratory time; T_E : expiratory time; T_{TOT} : total respiratory time.

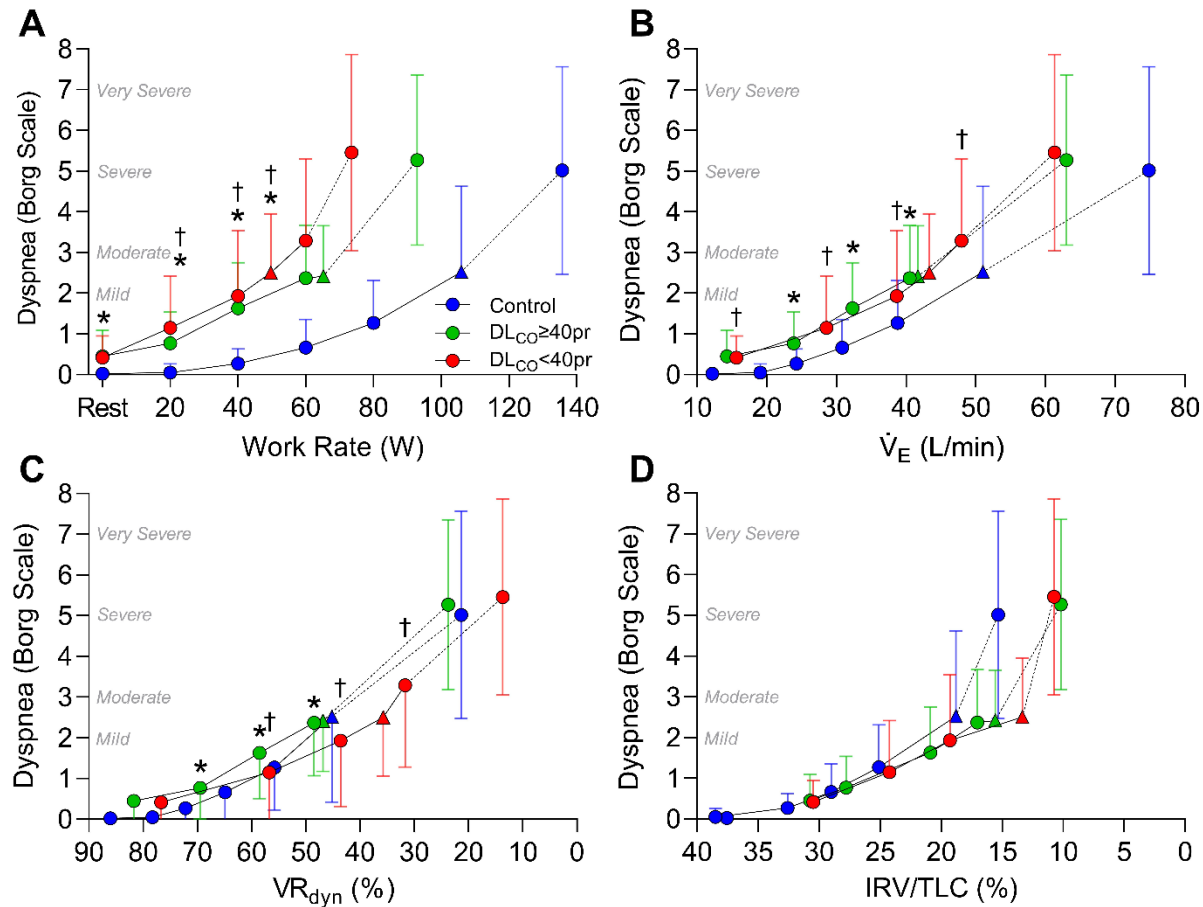


Figure 13. Dyspnea scores during incremental exercise. (*Chapter 4*)

Borg dyspnea scores as a function of exercise intensity (**A**), ventilatory output (**B**), and submaximal ventilatory (**C**) and volume (**D**) reserves in *f*-ILD patients with or without a severely decreased DL_{CO} (*red* and *green circles*, respectively) and sex- and age-matched healthy controls (*blue circles*). *Triangles* are values at the tidal volume inflection point, reflecting critically high inspiratory constraints. Data are mean ± standard deviation. *p*-values are for main-effect according to two-way ANOVA for repeated measures. Significant (*p*<0.05) Bonferroni adjusted post hoc between-group comparisons are indicated by: *: DL_{CO}≥40% predicted vs. controls; †: DL_{CO}<40% predicted vs. controls; ‡: DL_{CO}<40% predicted vs. DL_{CO}≥40% predicted. *Definition of abbreviations*: \dot{V}_E : expired minute ventilation; VR_{dyn}: dynamic ventilatory reserve; EILV: end-inspiratory lung volume; TLC: total lung capacity.

Chapter 5: Discussion and Concluding Remarks

Our studies enhanced the current understanding of the multiple respiratory and non-respiratory mechanisms that contribute to exertional symptoms – particularly dyspnea and poor exercise tolerance in patients with *f*-ILD of varied severity. *f*-ILD patients demonstrated consistently elevated dyspnea and lower exercise tolerance compared to healthy age- and sex-matched controls secondary to heightened ventilation. Throughout exercise, in both studies, *f*-ILD patients showed an increased demand to breathe (i.e., increased ventilation) and a reduced capacity of the respiratory system to meet that demand. For instance, [Figure 4](#) (*Study #1*, Chapter 3) and [Figure 13 C](#) (*Study #2*, Chapter 4) patients showed low submaximal breathing reserve compared to healthy controls and a tight relationship to increased dyspnea perception. However, previous studies focused on the restrictive nature of the disease as the primary reason for demand-capacity imbalance during exercise (Faisal et al., 2016; O'Donnell et al., 1998). While contributory, our results indicate that this approach overshadows other important abnormalities that could be therapeutic targets for reducing the symptom burden – including heightened leg discomfort e.g., cardiovascular and/or peripheral muscular impairment (*Study #2*). As a corollary, we found that, regardless of disease severity, DL_{CO} signaled more severe functional impairment, highlighting its relevance as a physiological biomarker.

5.1.1 The Role of Gas Exchange Impairment in Mild *f*-ILD

To gain a deeper understanding of the role of impaired pulmonary gas exchange in the genesis of dyspnea and exercise intolerance, we underwent a study on patients with *f*-ILD with preserved spirometry and only mild restriction on body plethysmography (*Study #1*). Of note, the normal spirometry contrasted with a consistent decrease in DL_{CO}. DL_{CO} is determined by 1) the alveolar-capillary surface area, 2) the volume of blood in the alveolar-capillary bed, and 3) the

distribution of \dot{V}_A , and thus provides a “*window*” into the pulmonary microvasculature (Hughes, 2003). In normoxic to mildly hypoxemic patients with minor fibrosis, a low DL_{CO} is more likely to reflect disturbances in \dot{V}_A - \dot{Q}_c matching rather than alveolar-capillary membrane thickening (Molgat-Seon et al., 2020). Thus, given that our patients have largely preserved lung volumes, \dot{V}_A / \dot{Q}_c mismatching, and an increased fraction of V_T wasted in the physiologic dead space were likely the chief causes of the high \dot{V}_E/\dot{V}_{CO_2} and low DL_{CO} in these patients.

During exercise, patients ventilated in excess of their metabolic demand ($\uparrow \dot{V}_E/\dot{V}_{CO_2}$), showing only mild exertional hypoxemia (between 93-95%) (Figure 2 A&C) suggesting that patients likely did not reach a low enough P_aO_2 (<60 mmHg) (Du Plessis et al., 2018) to elicit marked carotid body stimulation and thus a heightened ventilatory response secondary to carotid body stimulation (Dempsey & Wagner, 1999). However, patients’ heightened ventilatory response was associated with an increased demand-capacity imbalance of the respiratory system as demonstrated by earlier encroachment on the limits of key physiological ratios (i.e., lower submaximal breathing reserve ($\uparrow \dot{V}_E/MVV$; maximal voluntary ventilation) and restricted limits for V_T expansion (\downarrow IRV) (Figure 3 E and Figure 4, respectively), a finding shared by other studies in ILD (Milne et al., 2020b; Schaeffer et al., 2018) and other chronic respiratory diseases (Moore et al., 2018; Phillips et al., 2021b). Given patients’ preserved spirometry, these findings emphasize the importance of more advanced PFTs and CPETs in the investigation of exercise intolerance in the initial stages of *f*-ILD (Neder, 2023).

5.1.2 The Underpinnings of Exercise Intolerance in *f*-ILD Patients with a Severely Impaired DL_{CO}

Once we had clarified the relevance of DL_{CO} as a marker of gas exchange impairment and exercise intolerance in the initial stages of *f*-ILD (*Study #1*), *Study # 2* was planned to investigate

the meaning of a severely reduced DL_{CO} in patients with advanced *f*-ILD. Briefly, we found that a severely impaired DL_{CO} signals multiple interconnected systemic abnormalities (including disturbed hemodynamics, a precocious shift to skeletal muscle anaerobic metabolism, excess exertional ventilation secondary to heightened afferent stimuli, and critically high inspiratory constraints), which ultimately led to intolerable respiratory (dyspnea) and peripheral (leg discomfort) symptoms. These complex relationships are depicted in [Figure 14](#). Thus, this study shed novel light on the physiological and sensory mechanisms by which a severely reduced DL_{CO} (<40%) signals more pronounced exercise impairment in *f*-ILD.

5.1.3 Future Directions

These studies highlight the importance of gas exchange impairment in developing heightened dyspnea and worse exercise tolerance. As previously mentioned, arterial blood gas homeostasis is maintained through the appropriate matching of \dot{V}_A/\dot{Q}_c to minimize 1) distribution of air to poorly perfused alveolar units, reducing dead space, and 2) distribution of blood flow to poorly ventilated alveolar units, reducing venous admixture (J. A. Neder et al., 2022a). A mechanism by which \dot{V}_A/\dot{Q}_c matching can be disturbed is through inflammatory destruction of the capillary beds resulting in reduced perfusion to functional alveolar units. This process is usually irreversible; however, recent work in chronic obstructive pulmonary disease has looked at inhaled nitric oxide (iNO, a selective pulmonary vasodilator) as a therapeutic intervention aimed at improving gas exchange (Phillips et al., 2021a).

There is conflicting evidence surrounding the effectiveness of vasodilator therapies in ILD. Previous work using multiple inert gas elimination techniques in patients with IPF (seemingly in the moderate to late stages of the disease) looked at iNO on pulmonary hemodynamics and gas exchange and saw no difference (Blanco et al., 2011). Theoretically, this intervention may also

worsen dyspnea and exercise intolerance in some ILD patients. Remodeling of the capillary network through hypoxic pulmonary vasoconstriction seeks to prevent blood flow to poorly ventilated alveoli and global dilation of the pulmonary capillary network through the use of medications such as iNO may worsen gas exchange by reversing this attempt at vascular remodeling (Zangiabadi et al., 2014). Conversely, other studies in IPF have found statistical improvement in outcomes such as DL_{CO}, dyspnea, oxygen saturation, and quality of life using the vasodilator sildenafil (Harari et al., 2018; Zisman et al., 2010). This conflicting evidence suggests that there may be a context in which vasodilator therapy is more effective in some ILD patients, and future work should be conducted to better identify patients with greater pulmonary vascular impairment.

Following this concept, the DL_{CO} has the potential to help highlight a specific phenotype of *f*-ILD patients that may derive particular benefit from interventions targeting the pulmonary vasculature. As previously discussed, lung volumes are an essential consideration in the interpretation of a low DL_{CO} (Kaminsky et al., 2007; Stam et al., 1991). In advanced *f*-ILD, the combination of reduced lung volumes and perfusion abnormalities complicate the interpretation of a low DL_{CO}, blurring their relative contributions (King et al., 2011; Stam et al., 1991). Further, patients with a low DL_{CO} and severely impaired lung volumes are unlikely to benefit as much from pharmacological manipulation of the pulmonary vasculature compared to those with a low DL_{CO} and preserved lung volumes because impaired ventilation distribution also plays a significant role in gas exchange (Blanco et al., 2011). The utilization of CPET could improve the role of DL_{CO} in signaling vascular abnormalities by excluding patients with moderate to severe mechanical restriction and hypoxemia, exposing an *f*-ILD phenotype that might derive particular benefit from vasodilator therapy. To test this hypothesis, a large, controlled crossover study using iNO during

CPET should be conducted in *f*-ILD patients with a low DL_{CO} and normal to mild mechanical abnormalities and hypoxemia during CPET.

Experimental imaging models such as hyperpolarized 129-xenon MRI (Wang et al., 2018) and oxygen-enhanced MRI (Müller et al., 2002; Ohno et al., 2014) have shown a strong relationship between low DL_{CO} and signal intensity values in ILD patients and may be able to provide important insights into the lung structure-function assessment of patients with a low DL_{CO}. If validated, further research should be conducted using these MRI techniques in *f*-ILD patients with reduced DL_{CO} and largely preserved resting spirometry to explore the underlying causes of gas exchange inefficiency and determine whether vasodilator therapy would be effective for reducing exertional dyspnea in carefully selected patients.

5.2 Concluding Remarks

The results of the studies presented herein enhance our understanding of DL_{CO} as a physiological biomarker of activity-related impairment across the spectrum of *f*-ILD disease severity. Both studies support the current construct that demand-capacity imbalance is paramount to the genesis of exertional dyspnea. Moreover, they also provide a holistic view of the interconnected systemic abnormalities associated with exercise intolerance in *f*-ILD. This might have important implications for better phenotyping of *f*-ILD patients vis-à-vis the identification of patients who are likely to derive greater functional benefit from interventions targeting pulmonary gas exchange inefficiency. Moreover, our data strongly support DL_{CO} as the key index of physiologic impairment from early to end-stage *f*-ILD.

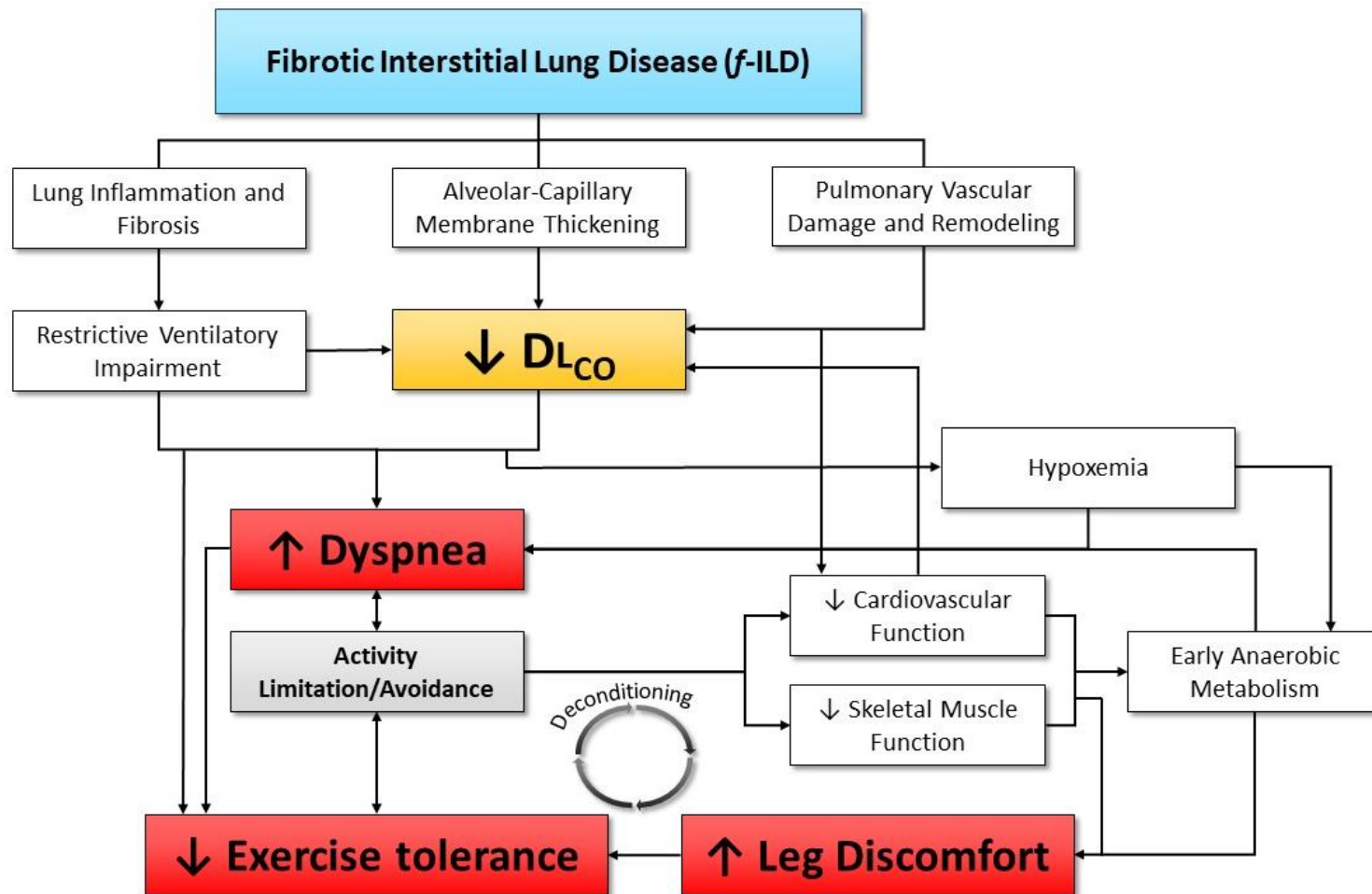


Figure 14. A holistic schematic of the systemic abnormalities signaled by a low diffusion capacity of the lung for carbon monoxide (DL_{CO}). (Chapter 5)

A holistic representation of the mechanisms by which a low diffusion capacity of the lung for carbon monoxide (DL_{CO}) signals multiple interconnected pathophysiologic features, including ventilatory impairment secondary to lung inflammation and fibrosis causing restriction, alveolar-capillary membrane thickening, pulmonary vascular damage and remodeling (i.e., \dot{V}_A/\dot{Q}_c mismatching secondary to capillary damage and hypoxic pulmonary vasoconstriction), and hypoxemia which ultimately leads to worse dyspnea intensity and poor exercise tolerance in patients with *f*-ILD. ↑=increased; ↓=decreased.

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Appendix A : Copywrite Permission of use Letter for Study #1 from Respiratory Care

(Request Number: 230823-031154)

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Dear Reginald Smyth

We hereby grant you permission to reprint the material below at no charge in your thesis subject to the following conditions:

RE: Physiological underpinnings of exertional dyspnoea in mild fibrosing interstitial lung disease, Respiratory Physiology & Neurobiology, Volume 312, 2023, Smyth et al.

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Appendix B : Health Sciences and Affiliated Teaching Hospitals

Research Ethics Board Approval for Study #1



QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW

November 27, 2013

Dr. D. E. O'Donnell
Department of Medicine
Queen's University

Dear Dr. O'Donnell

Study Title: DMED-1659-13 Respiratory Investigation Unit exercise test database

File # 6011437

Co-Investigators: Dr. J.A. Neber

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # **6011437** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6011437** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert J. Clark.

Chair, Health Sciences Research Ethics Board
November 27, 2013

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

Appendix C : Copywrite Permission of use Letter for Study #2 from Respiratory Care (Order License: 1394047-1)



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Appendix D : Health Sciences and Affiliated Teaching Hospitals

Research Ethics Board Approval for Study #2



QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW

November 27, 2013

Dr. D. E. O'Donnell
Department of Medicine
Queen's University

Dear Dr. O'Donnell

Study Title: DMED-1659-13 Respiratory Investigation Unit exercise test database

File # 6011437

Co-Investigators: Dr. J.A. Neber

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Yours sincerely,

A handwritten signature in cursive script that reads "Albert J. Clark".

Chair, Health Sciences Research Ethics Board
November 27, 2013

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete