ERJ open research

THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Original research article

Exercise responses and mental health symptoms in COVID-19 survivors with dyspnoea

Kathryn M. Milne, Juthaporn Cowan, Michele R. Schaeffer, Nha Voduc, Vicente Corrales-Medina, Kim L. Lavoie, Julio A. Chirinos, Joseph H. Puyat, Sara J. Abdallah, Jordan A. Guenette

Please cite this article as: Milne KM, Cowan J, Schaeffer MR, *et al*. Exercise responses and mental health symptoms in COVID-19 survivors with dyspnoea. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00606-2022).

Exercise responses and mental health symptoms in COVID-19 survivors with dyspnoea

Kathryn M. Milne[1,2], Juthaporn Cowan[3,4,5], Michele R. Schaeffer[1,6], Nha Voduc[3], Vicente Corrales-Medina[4], Kim L. Lavoie[7,8], Julio A. Chirinos[9], Joseph H. Puyat[10], Sara J. Abdallah[4], Jordan A. Guenette[1,2,6]

[1]Centre for Heart Lung Innovation, The University of British Columbia and Providence Research, St. Paul's Hospital, Vancouver, Canada
[2]Division of Respiratory Medicine, The University of British Columbia, Vancouver, Canada
[3]Department of Medicine, University of Ottawa, Ottawa, Canada
[4]Clinical Epidemiology Program, The Ottawa Hospital Research Institute, Ottawa, Canada
[5]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Canada
[6]Department of Physical Therapy, The University of British Columbia, Vancouver, Canada
[7]Montréal Behavioural Medicine Centre, CIUSSS du Nord-de-l'Île-de-Montréal, Montréal, Canada
[8]Department of Psychology, University of Québec at Montréal, Montréal, Canada
[9]Division of Cardiovascular Medicine, University of Pennsylvania, Philadelphia, United States
[10]Centre for Health Evaluation and Outcome Sciences, Providence Research, St. Paul's Hospital, Vancouver, Canada

Corresponding author: Jordan A. Guenette, Centre for Heart Lung Innovation, 166-1081 Burrard Street, Vancouver, BC, V6Z 1Y6; jordan.guenette@hli.ubc.ca

Author contributions: KMM, SJA and JAG conceived the study. JC, NV, VCM, KLL, JAC and SJA participated in data collection. KMM performed statistical analysis and wrote the first draft of the manuscript. KMM and JAG wrote the final draft of the manuscript. All authors contributed significantly to revision of the manuscript.

Running title: Mechanisms of persistent dyspnoea post-COVID-19

Keywords: dyspnoea, exercise test, COVID-19, respiratory physiology

Take home message: COVID-19 survivors experience specific qualitative dyspnoea sensations. Dyspnoea post-COVID-19 is related to abnormal pulmonary gas exchange and deconditioning and is linked to increased symptoms of anxiety, depression, and post-traumatic stress.

Word count: 2999

ABSTRACT

Objectives: Dyspnoea is a common persistent symptom post-coronavirus disease-19 (COVID-19) illness. However, mechanisms underlying dyspnoea in the post-COVID-19 syndrome remain unclear. The aim of our study was to examine dyspnoea quality and intensity, burden of mental health symptoms, and differences in exercise responses in people with and without persistent dyspnoea following COVID-19.

Methods: 49 participants with mild-to-critical COVID-19 were included in this cross-sectional study 4 months following acute illness. Between group comparisons were made in those with and without persistent dyspnoea (defined as modified Medical Research Council dyspnoea score ≥1). Participants completed standardized dyspnoea and mental health symptom questionnaires, pulmonary function tests, and incremental cardiopulmonary exercise testing.

Results: Exertional dyspnoea intensity and unpleasantness were increased in the dyspnoea group. The dyspnoea group described dyspnoea qualities of suffocating and tightness at peak exercise ($P<0.05$). Ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) nadir was higher (32±5 vs. 28±3, $P<0.001$) and anaerobic threshold was lower (41±12 vs. 49±11%predicted maximum oxygen uptake, $P=0.04$) in the dyspnoea group, indicating ventilatory inefficiency and deconditioning in this group. The dyspnoea group experienced greater symptoms of anxiety, depression, and post-traumatic stress (all

$P<0.05$). A subset of participants demonstrated gas-exchange and breathing pattern abnormalities suggestive of dysfunctional breathing.

Conclusions: People with persistent dyspnoea following COVID-19 experience a specific dyspnoea quality phenotype. Dyspnoea post-COVID-19 is related to abnormal pulmonary gas exchange and deconditioning and is linked to increased symptoms of anxiety, depression, and post-traumatic stress.

Word count: 234

INTRODUCTION

Persistent symptoms following coronavirus disease 2019 (COVID-19), termed post-COVID syndrome, represent an important clinical challenge [1]. Studies examining persistent symptoms following acute COVID-19 have used varying symptom and temporal definitions, resulting in large reported ranges (4.7-80%) of individuals developing this syndrome [2]. Dyspnoea is common post-COVID-19 infection, estimated to occur in ~40% of people [2]. Lasting dyspnoea is variably associated with severity of acute illness, age, female sex, and number of comorbidities [2]. Moreover, abnormal resting lung function, imaging abnormalities, and reduced functional capacity are not consistently associated with persistent dyspnoea [3]. Recent studies have described heterogenous clusters within the broader post-COVID syndrome, raising the possibility that mechanisms underlying dyspnoea in this population may be diverse [3, 4].

Cardiopulmonary exercise testing (CPET) has proved to be a valuable tool for characterizing the pathophysiology of exertional dyspnoea across cardiopulmonary, neurologic, and metabolic diseases. Most studies that have performed CPET in COVID-19 survivors have focused on comparing individuals with and without exercise intolerance [5], stratified participants by severity of acute illness [6-8], lung function impairment [9], or presence of imaging abnormalities [10]. Mechanisms of reduced exercise capacity described in available studies include: deconditioning [6, 9], ventilatory limitation [6, 7, 9], cardiac limitation [6], ventilatory inefficiency [6], and hyperventilation [4, 9, 11]. Importantly, no studies to our knowledge have examined dyspnoea intensity and quality, mental health symptoms, and exercise responses in combination. Therefore, the aim of our study was to examine dyspnoea quality and intensity, burden of mental health symptoms, and differences in exercise responses in participants with and without persistent dyspnoea following COVID-19. We hypothesized that people with persistent dyspnoea following COVID-19 infection would have a greater burden of mental health symptoms as well as abnormal gas-exchange during exercise. This study is a sub-group analysis of the larger Long-term Effect of SARS coronavirus 2 infection (LEFT) study on physiological and psychological health [12] and describes results related to persistent dyspnoea and mental health symptoms not previously reported.

METHODS

Study participants

Included participants were ≥18 years of age and were diagnosed with SARS coronavirus 2 infection causing COVID-19 illness by positive nasopharyngeal swab reverse transcription polymerase chain reaction prior to study participation. People who were unable to perform CPET on a cycle ergometer, had a diagnosis of current malignancy, or had self-reported pre-existing cardiopulmonary disease that could contribute to exertional dyspnoea (e.g. asthma, interstitial lung disease, pulmonary hypertension, heart failure), had a contraindication to exercise testing, or were treated with ambulatory oxygen were excluded from analysis. The study was approved by The Ottawa Health Science Network Research Ethics Board (20200371-01H). All participants provided written informed consent.

Study design

This is a cross-sectional sub-group analysis of the LEFT study on physiological and psychological health [12]. Pulmonary function testing and incremental CPET were performed in hospitalized individuals ~3-months post-discharge and non-hospitalized individuals 3-months after positive SARS coronavirus 2 test. Participants were stratified into those with and without persistent dyspnoea, defined as a modified Medical Research Council (mMRC) dyspnoea score ≥1.

Study procedures

Pulmonary function testing

Spirometry, body plethysmography, diffusing capacity of the lungs for carbon monoxide (D_LCO), and maximum inspiratory (MIP) and expiratory mouth pressures were performed in accordance with international guidelines using automated equipment (Vmax 229d with Vs62j body plethysmograph; SensorMedics; California, USA) [13-16]. Results are reported as absolute values and % predicted normal values [17-19].

Cardiopulmonary exercise testing

CPET was performed on an upright cycle ergometer (Ergoline 800s; SensorMedics; California, USA) using a breath-by-breath CPET system (Vmax229d; SensorMedics; California, USA) [20]. Results are expressed as absolute values and % predicted [21]. CPET consisted of a 3-minute resting period, followed by a 1-minute warm-up of unloaded pedaling, then 15W/minute stepwise increases in work rate to symptom limitation. Results were assessed for meeting maximal test criteria [22]. Standard cardiorespiratory variables were averaged every 30 seconds during exercise. Operating lung volumes were derived from inspiratory capacity (IC) maneuvers collected every 2 minutes. Highest equivalent submaximal work rate (HEWR) was defined as the 30 second increment achieved by all participants during CPET. Peak exercise was defined as the highest work rate maintained for 30 seconds. Ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) nadir was the lowest value measured during a 30 second increment during exercise. Anaerobic threshold (AT) was identified using the dual criteria method and expressed as a percentage of predicted maximum oxygen uptake ($\dot{V}O_2$) [20]. Possible dysfunctional breathing was identified if a participant met any 1 of 3 criteria including gas-exchange ($P_{ET}CO_2$ <30 mmHg at rest and exercise; $\dot{V}_E/\dot{V}CO_2$ >35 at submaximal work rate [60W]) or erratic breathing pattern abnormalities [23].

Symptom evaluation

Diverse domains of dyspnoea including symptom intensity, associated affective distress, and sensory-perceptual experience of the participant were collected by validated questionnaires. Dyspnoea intensity and unpleasantness as well as leg discomfort were rated at rest, every 2 minutes throughout exercise, and at peak exercise using the modified 0-10 category ratio Borg scale [24]. Dyspnoea intensity and unpleasantness were described to participants using a standardized script frequently used in dyspnoea research [25]. Individuals verbalized their main reasons for stopping exercise and if applicable, described the proportion to which dyspnoea or leg discomfort contributed to exercise limitation. Qualitative descriptors of respiratory discomfort were collected by questionnaire (**Supplementary Table 1**) [26]. Dyspnoea/ventilation ($\dot{V}_E$) and dyspnoea unpleasantness/$\dot{V}_E$ slopes were calculated using linear regression from rest to peak exercise excluding zero values.

Validated questionnaires were used to assess: dyspnoea using the Dyspnoea-12 and mMRC [27, 28], stress using the Perceived Stress Scale [29], anxiety sensitivity using the Anxiety Sensitivity Index-Revised [30], symptoms associated with post-traumatic stress disorder (PTSD) using the Impact of Event Scale - Revised [31], anxiety and depression using the Hospital Anxiety and Depression scale [32], and quality of life using the St. George’s Respiratory Questionnaire [33].

Statistical analysis

Independent t-tests with Bonferroni correction for multiple comparisons at *a priori* defined exercise work rates were used to make between group comparisons in exercise responses. Independent t-tests and Fisher's exact tests were used to compare post-COVID-19 dyspnoea and non-dyspnoea groups for continuous and categorical variables, respectively. Spearman's correlation was used to characterize bivariate relationships between dyspnoea intensity and unpleasantness at HEWR with mental health symptom scores and physiologic variables. Best subset multivariable linear regression was used to explore associations between variables of interest and dyspnoea intensity and unpleasantness measured at HEWR using the 0-10 category ratio Borg scale. Statistical significance was defined as $P<0.05$. Data are presented as mean ± standard deviation unless otherwise indicated. Statistical analyses were performed in SPSS (SPSS v27, IBM) and RStudio.

RESULTS

Study participants

Recruitment for the LEFT study took place between June and October 2020 as previously described [12]. A total of 62 participants with complete CPET data were available for sub-study inclusion. After excluding participants with pre-existing cardiopulmonary disease or current malignancy, a total of 49 participants were included in the study and final analysis. There were 26 participants in the dyspnoea group and 23 participants in the non-dyspnoea group. There was no age difference between included and excluded participants, although more males were excluded based on exclusion criteria. Included participants were diagnosed with COVID-19 between March to June 2020. Participants performed CPET 125±18 days following acute COVID-19 diagnosis. Participant demographic, anthropomorphic, COVID-19 illness, and questionnaire results are summarized in **Table 1**.

Most study participants self-identified as Caucasian. Both groups were overweight and the proportion of female and males was similar between groups (**Table 1**). There were no current cigarette smokers in either group. The number of participants with a self-reported psychiatric diagnosis was similar between groups (3/26 dyspnoea group, 1/23 non-dyspnoea group). Number of participants taking an anti-anxiety or anti-depressant medication was not available. Frequency of common medical comorbidities were similar (**Table 1**). Many people in both groups were treated as outpatients. There was no difference in the number of participants that received therapeutic anticoagulation during their hospitalization between groups (12% dyspnoea group vs. 17% non-dyspnoea group, *P*=0.69). Only 3 participants in each group received glucocorticoid steroid.

Resting pulmonary function tests

Pulmonary function test results are presented in **Table 1**. One participant in the non-dyspnoea group had a forced expiratory volume in 1 second/forced vital capacity

(FEV_1/FVC) below the lower limit of normal (LLN). Total lung capacity (TLC) was below the LLN in 27% of the dyspnoea participants and 9% of the non-dyspnoea participants (*P*=0.15). People in each group had D_LCO below the LLN (32% dyspnoea group vs. 22% non-dyspnoea group, *P*=0.52). The proportion of participants with MIP below thresholds associated with higher likelihood of respiratory muscle weakness [34] was greater in the dyspnoea group (19% dyspnoea group vs. 9% non-dyspnoea group), although this was not significant (*P*=0.42).

Symptom evaluation

Dyspnoea

During CPET, submaximal dyspnoea intensity (**Figure 1A**) and unpleasantness (**Figure 1B**) were higher in the dyspnoea group. Dyspnoea unpleasantness was higher at peak exercise in the dyspnoea group, at peak VO_2 37% lower than that achieved by the non-dyspnoea group. Submaximal leg discomfort was also elevated in the dyspnoea group (**Figure 1C**). Dyspnoea intensity/$\dot{V}_E$ slope tended to be higher in the dyspnoea group (0.16±0.16 vs. 0.10±0.05 Borg 0-10/$L \cdot min^{-1}$) but this did not reach statistical significance (*P*=0.11). Dyspnoea unpleasantness/$\dot{V}_E$ slope was greater in the dyspnoea group (0.17±0.16 vs. 0.09±0.07 Borg 0-10/$L \cdot min^{-1}$, *P*=0.03). Qualitative dyspnoea descriptive clusters were different between dyspnoea and non-dyspnoea groups (**Figure 2**), with unsatisfied inspiration, inspiratory difficulty, suffocating and tightness sensations more frequently described in the dyspnoea group.

Mental health associated symptoms and quality of life

Participants with persistent dyspnoea had higher anxiety and depression scores and lower quality of life in comparison to their counterparts without dyspnoea (**Table 1**). The dyspnoea group exhibited higher levels of perceived stress and experienced greater panic-like anxiety in comparison to those without dyspnoea and reported reference values [29, 30, 35]. Participants with dyspnoea additionally experienced symptoms of PTSD similar to those reported in people recovering from motor vehicle accidents [31].

Exercise responses

All participants met at least one criteria for a maximal CPET [22]. Peak exercise and HEWR results are presented in **Table 2**. Peak $\dot{V}O_2$ (**Figure 3A**) and work rate were lower in the dyspnoea group. Dyspnoea and leg fatigue contributed to exercise limitation in both groups. Dyspnoea was rated as contributing to exercise limitation to a greater extent in the dyspnoea group (51±35% dyspnoea group vs. 39±33% non-dyspnoea group) although not statistically significant (*P*=0.26).

The dyspnoea group had evidence of abnormal pulmonary gas exchange during exercise with ventilatory inefficiency (higher $\dot{V}_E/\dot{V}CO_2$) and lower partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) during exercise (**Figure 4B** and **4C**, **Figure 5C**). At HEWR, dyspnoea intensity was higher in the dyspnoea group (**Figure 5A**). $\dot{V}_E/\dot{V}CO_2$

nadir was higher in the dyspnoea group (**Figure 5D**), which occurred in the absence of significant desaturation (**Figure 4A**) during exercise. There was no significant difference between groups in the frequency of possible dysfunctional breathing; however, there were more possible cases in the dyspnoea group (38% dyspnoea group vs. 22% non-dyspnoea group, *P*=0.233).

There were no overall differences in ventilation or breathing pattern (**Figure 3D, E, F**). Despite a greater proportion of individuals in the dyspnoea group with TLC<LLN, there was no evidence of abnormal dynamic respiratory mechanics or development of critical respiratory constraint throughout (**Figure 4D, E, F**) or at peak exercise (**Table 2**). Cardiovascular responses were similar (**Figure 3B** and **C**, **Table 2**) between groups, although O_2 pulse tended to be lower and heart rate reserve was greater in the dyspnoea group (**Table 2**). The AT occurred at a lower percentage of predicted VO_2max in the dyspnoea group (**Figure 5B**).

Correlates and predictors of dyspnoea

When all participants were pooled together, dyspnoea unpleasantness at HEWR (*r*=-0.370, *P*=0.010), but not intensity (*r*=-0.223, *P*=0.128), was correlated with lower D_LCO (*r*=-0.370, *P*=0.010). Both dyspnoea intensity (*r*=-0.346, *P*=0.015) and unpleasantness (*r*=-0.366, *P*<0.001) were associated with ventilatory inefficiency. Dyspnoea unpleasantness was additionally associated with lower anaerobic threshold (*r*=-0.162, *P*=0.007). Both dyspnoea intensity and unpleasantness were associated with greater burden of mental health symptoms.

Best subset multivariable linear regression models were constructed for dyspnoea intensity and unpleasantness (**Supplementary Table 2**). Physiologic, mental health, and quality of life variables were included in the model. Sex, age, smoking pack years, and BMI were included in the model as potential confounders. The model did not predict dyspnoea intensity, adjusted R^2=0.357, $F(13,8)$=1.897, P=0.184, despite $\dot{V}_E/\dot{V}CO_2$ nadir and perceived stress being related to dyspnoea intensity. Although $\dot{V}_E/\dot{V}CO_2$ nadir was related to dyspnoea unpleasantness (**Supplementary Table 2**), the overall model did not significantly predict dyspnoea unpleasantness, adjusted R^2=0.463, $F(13,8)$=2.394, P=0.110.

DISCUSSION

To our knowledge, this is the first study to simultaneously examine differences in both the intensity and qualitative dimensions of exertional dyspnoea, burden of mental health symptoms, and exercise responses in people with and without persistent breathlessness following COVID-19. Participants with persistent dyspnoea had a higher burden of mental health symptoms related to anxiety, depression, and PTSD, and lower quality of life compared to their counterparts without dyspnoea. Importantly, dyspnoea quality in this group was characterized by increased unpleasantness and sensations of suffocating and tightness. Participants with persistent dyspnoea demonstrated reduced peak exercise $\dot{V}O_2$ and work rate, abnormalities of gas exchange with increased ventilatory inefficiency, as well as a lower AT and increased heart rate reserve in comparison to their counterparts without dyspnoea. Altered exercise responses were uncovered during CPET in these people with preserved resting lung function. Collectively, our results demonstrate that persistent dyspnoea post-COVID-19 is related to abnormal pulmonary gas exchange and deconditioning, and is associated with symptoms of anxiety, depression, and PTSD.

We demonstrate that dyspnoea unpleasantness is increased and not explained as a function of relatively greater ventilation during exercise in people with chronic breathlessness and significant mental health symptoms. Dyspnoea was described as suffocating in over 50% and tightness in approximately 40% of participants in the dyspnoea group. These are not common descriptors of breathlessness at peak exercise in health or other chronic respiratory diseases such as chronic obstructive pulmonary disease or interstitial lung disease where dyspnoea is more frequently described as inspiratory difficulty and unsatisfied inspiration [26, 36, 37]. Although not significant, there were more participants that met criteria for possible dysfunctional breathing in the dyspnoea group. The interaction between afferent signals of impaired pulmonary gas exchange, breathing pattern, and increased mental health symptoms in the integrated experience of dyspnoea is not completely understood. Our novel results demonstrate dyspnoea qualities in COVID-19 survivors are different from some chronic respiratory diseases and underscores the importance of a multidimensional assessment that considers both dyspnoea intensity, unpleasantness and quality.

A minority of studies have examined exercise responses in COVID-19 survivors and fewer still have included measurement of exertional dyspnoea during CPET. Baratto *et al*. [38] demonstrated that COVID-19 survivors had reduced $\dot{V}O_2$ peak, impaired peripheral oxygen extraction, and ventilatory inefficiency. Ventilatory inefficiency was attributed by the authors to altered chemosensitivity in most subjects with a minority having increased dead space [38]. Increased $\dot{V}_E/\dot{V}CO_2$ has been described in people hospitalized for COVID-19 with dyspnoea 3-6 months following acute illness, consistent with our results [6, 8]. Operating lung volumes during CPET showed no evidence of significant respiratory mechanical constraints in another study [38]. This is also demonstrated by our participants studied at 4 months into recovery, despite reduced TLC in a proportion of participants.

Both dyspnoea intensity and unpleasantness were correlated with ventilatory inefficiency on bivariate analysis. Ventilatory inefficiency may be related to either increased physiological dead space or increased chemosensitivity and alveolar hyperventilation, alone or in variable combination [39]. Hyperventilation during exercise in COVID-19 survivors has been variably defined in available studies to date [9], with a paucity of studies employing arterial blood gas measurements [4, 7, 11, 38]. A study by Singh *et al*. [11] using invasive CPET in 10 people recovering from mild acute COVID-19 illness with persistent symptoms at 11 months found that increased $\dot{V}_E/\dot{V}CO_2$ slope during exercise was not associated with increased physiological dead space and was related to hyperventilation and increased chemosensitivity. Hyperventilation as a consequence of alteration in the arterial carbon dioxide set point and increased chemosensitivity may occur in the setting of altered pH balance, hypoxemia, stimulation of baroreceptors within the pulmonary vasculature, or autonomic nervous system activation [39]. Hyperventilation has additionally been described in people with dysfunctional breathing syndromes associated with anxiety [40]. We did not employ arterial blood gas measurements, but the association of increased dyspnoea intensity and unpleasantness with greater burden of mental health symptoms raises the possibility that multiple mechanisms may account for increased $\dot{V}_E/\dot{V}CO_2$ in the post-COVID syndrome including dysfunctional breathing syndromes.

Although we present unique data incorporating dyspnoea intensity and quality with exercise responses in COVID-19 survivors, our study has some limitations. Assessment of mental health symptoms and physical activity prior to COVID-19 infection was not possible. We also did not have access to a matched healthy control population. As previously mentioned, we did not employ arterial blood gas measurements and conclusions regarding the mechanisms of increased $\dot{V}_E/\dot{V}CO_2$ in our participants are therefore limited. Results of chest imaging were not available as a part of this study. Our moderate sample size limits further exploring heterogeneous physiological mechanisms contributing to dyspnoea between sub-groups (i.e. people with lower MIP, TLC<LLN, or suspected hyperventilation). Larger studies using CPET in addition to chest imaging will be needed to fully characterize phenotypes within the post-COVID syndrome.

We describe unique insights into persistent dyspnoea after acute COVID-19 illness in people with and without chronic breathlessness. Our work highlights the increased burden of mental health symptoms in COVID-19 survivors with persistent dyspnoea and associated dyspnoea qualities and unpleasantness experienced by these participants. People with dyspnoea and normal resting lung function exhibit gas-exchange abnormalities and reduced AT during CPET. Ventilatory inefficiency was more frequently observed in the dyspnea group in our study, and the relationship between ventilatory inefficiency and dyspnoea, as well as its multiple potential causes, requires further detailed physiologic study. Comprehensive care of the COVID-19 survivor will undoubtedly require attention and targeted interventions, which may include physiotherapy for dysfunctional breathing, pulmonary rehabilitation, occupational therapy, and medical therapies focused on both abnormal physiology contributing to dyspnoea as well as the increased burden of mental health comorbidity.

ACKNOWLEDGEMENTS

We thank our participants for enthusiastically volunteering for this study.

FUNDING

The study was funded by The Ottawa Hospital COVID-19 Emergency Response Fund. KMM was supported by a Michael Smith Health Research BC Postdoctoral Fellowship and a Transition to Faculty Award from the Faculty of Medicine Academic Enhancement Fund at The University of British Columbia.

TABLES

Table 1. Participant demographic, anthropomorphic, acute COVID-19, and pulmonary function characteristics comparing those with and without persistent dyspnoea.

Variable	Dyspnoea group	Non-dyspnoea group
Demographic and anthropomorphic		
Participants, n	26	23
Age, years	50±15	46±14
Sex, male:female	12:14	14:9
BMI, kg/m^2	29±7	28±6
Ever-smoker, n (%)	7 (27)	5 (22)
Smoking, pack years	10±12	4±3
Comorbidities		
Hypertension, n (%)	6 (23)	3 (13)
Atrial fibrillation, n (%)	2 (8)	2 (9)
Coronary artery disease, n (%)	1 (4)	1 (4)
Diabetes Me, n (%)	4 (15)	3 (13)
Dyslipidemia, n (%)	3 (12)	4 (17)
Hypothyroidism, n (%)	1 (4)	1 (4)
Arthritis, n (%)	1 (4)	2 (9)
OSA, n (%)	0 (0)	3 (13)
GERD, n (%)	3 (12)	0 (0)
Acute COVID-19 illness		
COVID-19 Severity		
Outpatient[a], n (%)	15 (58)	17 (74)
Hospitalized, n (%)	11 (42)	6 (26)
Hospitalized without supplemental oxygen, n	1	1
Supplemental oxygen in hospital, n	8	2
Invasive ventilation, n	2	3
Duration of hospitalization, days	7±14	6±15
Intensive care unit stay, n (%)	4 (15)	4 (17)
Duration of intensive care unit stay, days	12±5	19±18
Inpatient rehabilitation[b], n (%)	3 (12)	2 (9)
Symptoms and quality of life		
mMRC, 0-4 scale	1±1[†]	0±0
D-12 total	10.7±9.3[†]	0.5±1.6
D-12 physical	7.6±5.8[†]	0.5±1.5
D-12 affective	3.1±3.8[†]	0.0±0.2
HADS total	15.9±8.2*	8.3±7.1
HADS anxiety	9.4±4.9*	6.0±4.6
HADS depression	6.5±4.3[†]	2.3±2.8

SGRQ total	32.3±19.3†	8.6±8.7
SGRQ symptom	40.2±24.9†	14.5±14.5
SGRQ activity	53.7±26.3†	15.4±17.9
SGRQ impact	22.3±19.7†	2.8±5.5
PSS, score out of 40	18.6±6.5*	13.4±9.2
ASI-R, score out of 144	44.7±36.0*	21.6±20.3
IES-R total, 0-4 scale	1.5±1.1†	0.4±0.6
IES-R intrusion, 0-4 scale	1.6±1.2†	0.4±0.6
IES-R avoidance, 0-4 scale	1.5±1.0†	0.4±0.5
IES-R hyperarousal, 0-4 scale	1.4±1.2*	0.4±0.8
Pulmonary function		
FEV_1, % pred	96±16	95±10
FVC, % pred	98±17	101±13
FEV_1/FVC	0.79±0.06	0.76±0.05
TLC, % pred	90±16	95±12
VC, % pred	92±18	99±15
IC, % pred	92±23	94±17
RV, % pred	87±20	83±16
$D_{L}CO$, % pred	87±18	92±18
MIP, cmH$_2$O	76±29*	95±32
MEP, cmH$_2$O	81±27	100±41

Presented values are mean±standard deviation, unless otherwise specified. *$P<0.05$, $^{\dagger}P<0.001$. [a]Outpatient cases included participants that required no medical intervention or had an isolated visit to the emergency department without admission to hospital. [b]Inpatient rehabilitation consisted of admission to a rehabilitation focused hospital while undergoing intensive physical and occupational therapy rehabilitation.

Abbreviations: ASI-R, Revised Anxiety Sensitivity Index; BMI, body mass index; D-12, Dyspnoea-12 dyspnoea score; $D_{L}CO$, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; IC, inspiratory capacity; IES-R, Revised impact of Event Scale; MEP, maximum expiratory mouth pressure; MIP, maximum inspiratory mouth pressure; mMRC, modified Medical Research Council dyspnoea score; PSS, Perceived Stress Scale; RV, residual volume; SGRQ, St. George Respiratory Questionnaire; TLC, total lung capacity; VC, vital capacity.

Table 2. Select variables at highest equivalent work rate (30W) and peak exercise measured during incremental cardiopulmonary exercise test comparing COVID-19 survivors with and without persistent dyspnoea.

	HEWR		**Peak Exercise**	
Variable	**Dyspnoea group**	**Non-dyspnoea group**	**Dyspnoea group**	**Non-dyspnoea group**
$\dot{V}O_2$, L/min	0.52±0.18	0.54±0.19	1.51±0.53*	2.07±0.71
$\dot{V}O_2$, % pred	25±10	24±9	71±22*	86±16
$\dot{V}O_2$, mL/kg/min	6.5±2.5	6.5±2.1	18.5±5.9*	24.7±7.4
Work rate, W	30±0	30±0	130±49*	179±63
Work rate, % pred	20±5	18±5	85±29	102±19
$\dot{V}_E$, L/min	18.5±6.6	16.7±5.0	63.9±21.3	81.3±27.7
$\dot{V}_E$/MVC, %	19±9	15±6	60±14	67±14
V_T, L	0.86±0.29	0.93±0.32	1.71±0.57	2.18±0.66
*F*b, breath/min	23±7	20±6	38±8	38±7
RER	0.91±0.10	0.86±0.09	1.25±0.10	1.24±0.08
$P_{ET}CO_2$, mmHg	37±3*	39±2	35±5	36±3
SpO_2, %	97±1	97±1	97±2	97±1
V_D/V_T	0.27±0.06	0.26±0.06	0.17±0.06*	0.13±0.04
IC, L	2.81±0.75	3.14±0.73	2.75±0.81	3.18±0.93
IC, % pred	85±23	88±14	86±20	88±18
IRV, L	1.95±0.72	2.21±0.67	1.04±0.53	1.01±0.51
EILV/TLC, %	64±11	65±7	81±8	84±8
EELV/TLC %	48±10	49±6	49±9	49±7
HR, bpm	93±12	87±12	146±26	164±23
HRR, bpm			24±20*	10±14
HR, % pred	58±10	52±9	90±13	98±9
O_2 pulse, mL/beat	5.6±1.9	6.4±2.3	10.3±2.8	12.5±3.6
O_2 pulse, % pred	41±15	44±16	74±17	83±16
SBP, mmHg			164±18	174±21
DBP, mmHg			85±4	86±6
Dyspnoea intensity, 0-10 Borg scale	2.0±1.4*	0.9±1.1	7.6±2.1	7.0±2.1
Dyspnoea unpleasantness, 0-10 Borg scale	1.5±1.6	0.6±1.0	7.3±2.3*	5.3±2.7
Leg fatigue, 0-10 Borg scale	1.3±1.5	0.4±0.8	7.6±2.5	7.5±1.9

Presented values are mean±standard deviation, unless otherwise specified. *Signifies $P<0.05$ difference between groups following Bonferroni correction at the respective exercise intensity (HEWR or peak exercise).

Abbreviations: DBP, diastolic blood pressure; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; *F*b, breathing frequency; HEWR, highest equivalent work rate; HR, heart rate; HRR, heart rate reserve; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVC, maximum ventilatory capacity (FEV_1x35); $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation measured by finger pulse oximetry; TLC, total lung capacity; V_D/V_T, non-invasive estimation of dead space tidal volume ratio; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume.

REFERENCES

1. World Health Organization. 2023 [cited 2023 January 13]; Available from: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition

2. Iqbal FM, Lam K, Sounderajah V, *et al*. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine 2021: 36: 100899.

3. Evans RA, McAuley H, Harrison EM, *et al*. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med 2021; 9: 1275-1287.

4. Motiejunaite J, Balagny P, Arnoult F, *et al*. Hyperventilation: A Possible Explanation for Long-Lasting Exercise Intolerance in Mild COVID-19 Survivors? Front Physiol 2020: 11: 614590.

5. Rinaldo RF, Mondoni M, Parazzini EM, *et al*. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. Eur Respir J 2021: 58: 2100870.

6. Skjorten I, Ankerstjerne OAW, Trebinjac D, *et al*. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. Eur Respir J 2021: 58: 2100996.

7. Debeaumont D, Boujibar F, Ferrand-Devouge E, *et al*. Cardiopulmonary Exercise Testing to Assess Persistent Symptoms at 6 Months in People With COVID-19 Who Survived Hospitalization: A Pilot Study. Phys Ther 2021: 101: pzab099.

8. Aparisi A, Ybarra-Falcon C, Garcia-Gomez M, *et al*. Exercise Ventilatory Inefficiency in Post-COVID-19 Syndrome: Insights from a Prospective Evaluation. J Clin Med 2021: 10: 2591.

9. Motiejunaite J, Balagny P, Arnoult F, *et al*. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. Eur Respir J 2021: 58: 2101578.

10. Liu M, Lv F, Huang Y, Xiao K. Follow-Up Study of the Chest CT Characteristics of COVID-19 Survivors Seven Months After Recovery. Front Med (Lausanne) 2021: 8: 636298.

11. Singh I, Joseph P, Heerdt PM, *et al*. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest 2021: S0012-3692: 03635-7.

12. Abdallah SJ, Voduc N, Corrales-Medina VF, *et al*. Symptoms, Pulmonary Function, and Functional Capacity Four Months after COVID-19. Ann Am Thorac Soc 2021: 18(11): 1912-1917.

13. Graham BL, Brusasco V, Burgos F, *et al*. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017: 49: 1600016.

14. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. Eur Respir J 2005: 26: 319-338.

15. Wanger J, Clausen JL, Coates A, *et al*. Standardisation of the measurement of lung volumes. Eur Respir J 2005: 26: 511-522.

16. Laveneziana P, Albuquerque A, Aliverti A, *et al*. ERS statement on respiratory muscle testing at rest and during exercise. Eur Respir J 2019: 53: 1801214.

17. Gutierrez C, Ghezzo RH, Abboud RT, Cosio MG, Dill JR, Martin RR, McCarthy DS, Morse JL, Zamel N. Reference values of pulmonary function tests for Canadian Caucasians. Can Respir J 2004: 11(6): 414-424.

18. Quanjer PH, Stanojevic S, Cole TJ, *et al*. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012: 40: 1324-1343.

19. Stanojevic S, Graham BL, Cooper BG, *et al*. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J 2017: 50: 1700010.

20. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003: 167: 211-277.

21. Lewthwaite H, Benedetti A, Stickland MK, *et al*. Normative peak cardiopulmonary exercise rest responses in Canadian adults Aged >/=40 Years. Chest 2020: 158: 2532-2545.

22. Radtke T, Crook S, Kaltsakas G, *et al*. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir Rev 2019: 28: 180101.

23. Watson M, Ionescu MF, Sylvester K, *et al*. Minute ventilation/carbon dioxide production in patients with dysfunctional breathing. Eur Respir Rev 2021: 30: 200182.

24. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982: 14: 377-381.

25. Banzett RB, Pedersen SH, Schwartzstein RM, *et al*. The affective dimension of laboratory dyspnea: air hunger is more unpleasant than work/effort. Am J Respir Crit Care Med 2008: 177(12): 1384-1390.

26. Simon PM, Schwartzstein RM, Weiss JW, *et al*. Distinguishable types of dyspnea in patients with shortness of breath. Am Rev Respir Dis 1990: 142: 1009-1014.

27. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ 1960: 2: 1662.

28. Yorke J, Moosavi SH, Shuldham C, *et al*. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax 2010: 65: 21-26.

29. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983: 24: 385-396.

30. Taylor S, Cox BJ. An expanded anxiety sensitivity index: evidence for a hierarchic structure in a clinical sample. J Anxiety Disord 1998: 12: 463-483.

31. Weiss D, CR M. The impact of event scale - revised. Assessing psychological trauma and PTSD. Guildford Press, 1997.

32. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983: 67: 361-370.

33. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991: 85 Suppl B: 25-31; discussion 33-27.

34. Rodrigues A, Da Silva ML, Berton DC, *et al*. Maximal inspiratory pressure: Does the choice of reference values actually matter? Chest 2017: 152(1): 32-39.

35. Deacon BJ, Abramowitz JS, Woods CM, *et al*. The Anxiety Sensitivity Index - Revised: psychometric properties and factor structure in two nonclinical samples. Behav Res Ther 2003: 41: 1427-1449.

36. O'Donnell DE, Bertley JC, Chau LK, *et al*. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. Am J Respir Crit Care Med 1997: 155: 109-115.

37. O'Donnell DE, Chau LK, Webb KA. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. J Appl Physiol (1985) 1998: 84: 2000-2009.

38. Baratto C, Caravita S, Faini A, *et al*. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. J Appl Physiol (1985) 2021: 130: 1470-1478.

39. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. Am Rev Respir Dis 1984: 129: S17-20.

40. Boulding R, Stacey R, Niven R, *et al*. Dysfunctional breathing: a review of the literature and proposal for classification. Eur Respir Rev 2016: 25: 287-294.

FIGURE LEGENDS

Figure 1. Perceptual responses throughout exercise comparing dyspnoea and non-dyspnoea groups.

Values are mean ± standard deviation, *signifies $P<0.05$ difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants.

Abbreviations: HEWR, highest equivalent work rate.

Figure 2. Selection of qualitative dyspnoea descriptors at peak exercise comparing dyspnoea and non-dyspnoea groups.

*$P<0.05$.

Figure 3. Cardiopulmonary exercise test results comparing cardiovascular and ventilatory responses between dyspnoea and non-dyspnoea groups.

Values are mean ± standard deviation, *signifies $P<0.05$ difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent

HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants.

Abbreviations: *F*b, breathing frequency; HEWR, highest equivalent work rate; HR, heart rate; $\dot{V}O_2$, oxygen uptake; $\dot{V}_E$, minute ventilation; V_T, tidal volume.

Figure 4. Cardiopulmonary exercise test results comparing gas exchange and non-invasive respiratory mechanical responses between dyspnoea and non-dyspnoea groups.

Values are mean ± standard deviation, *signifies $P<0.05$ difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants.

Abbreviations: EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; HEWR, highest equivalent work rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; SpO_2, oxygen saturation measured by finger pulse oximetry; TLC, total lung capacity; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

Figure 5. Gas exchange, metabolic and dyspnoea intensity responses for individual participants with and without dyspnoea.

Bars represent mean ± standard deviation. Dyspnoea intensity and $P_{ET}CO_2$ values are presented at HEWR.

Abbreviations: AT, anaerobic threshold; HEWR, highest equivalent work rate; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_{2max}$, maximum oxygen uptake.

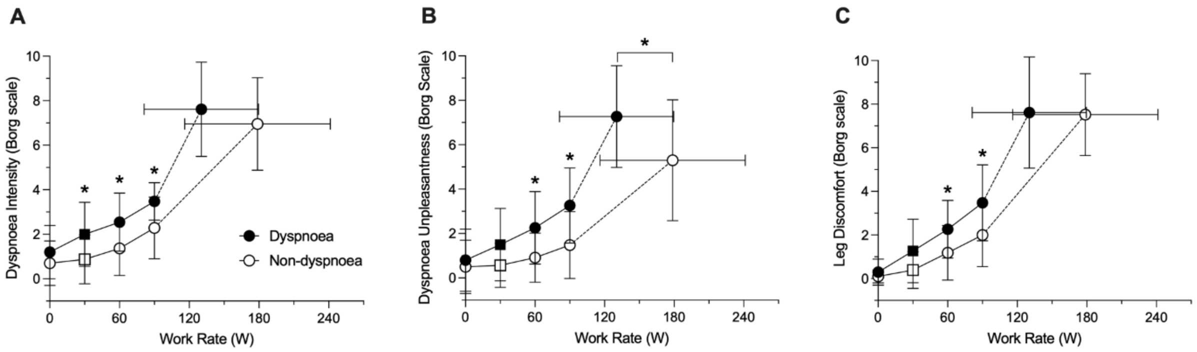

Figure 1. Perceptual responses throughout exercise comparing dyspnoea and non-dyspnoea groups.Values are mean±standard deviation, *signifies $P<0.05$ difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants.Abbreviations: HEWR, highest equivalent work rate.

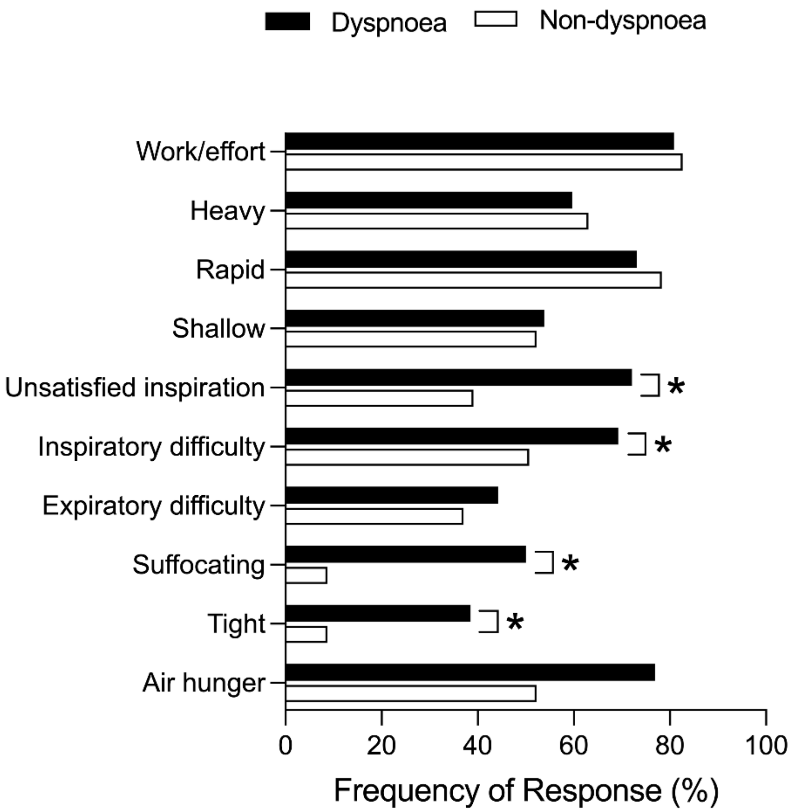

Figure 2. Selection of qualitative dyspnoea descriptors at peak exercise comparing dyspnoea and nondyspnoea groups. **P*<0.05.

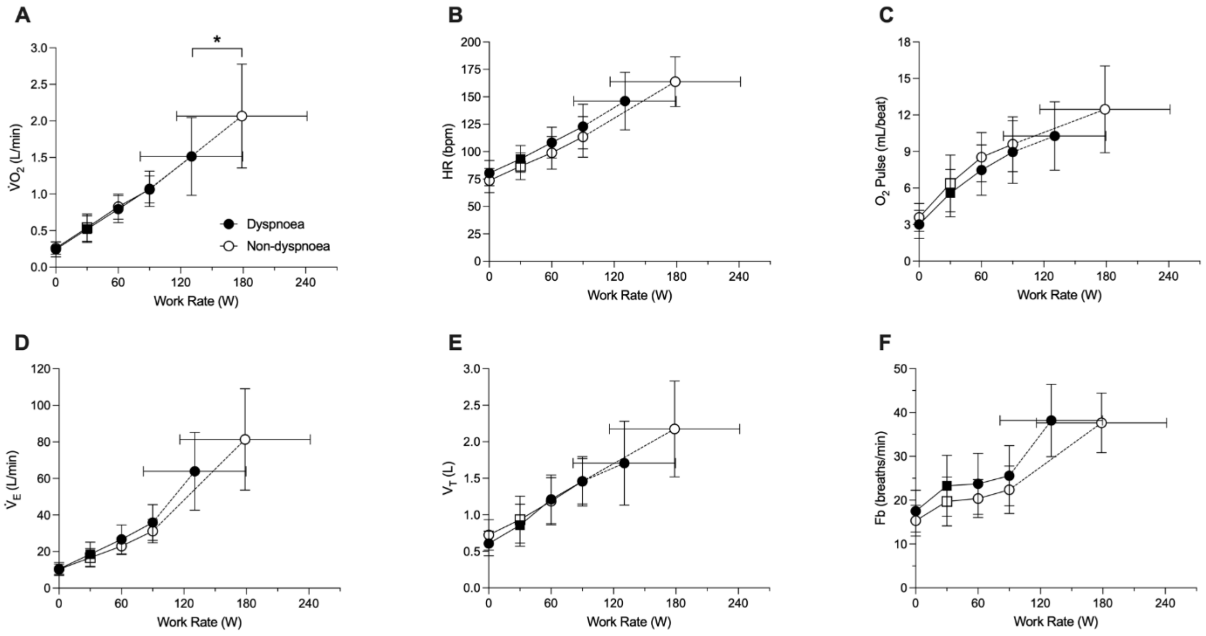

Figure 3. Cardiopulmonary exercise test results comparing cardiovascular and ventilatory responses between dyspnoea and non-dyspnoea groups. Values are mean±standard deviation, *signifies *P*<0.05 difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants. Abbreviations: *F*b, breathing frequency; HEWR, highest equivalent work rate; HR, heart rate; VO2, oxygen uptake; VE, minute ventilation; VT, tidal volume.

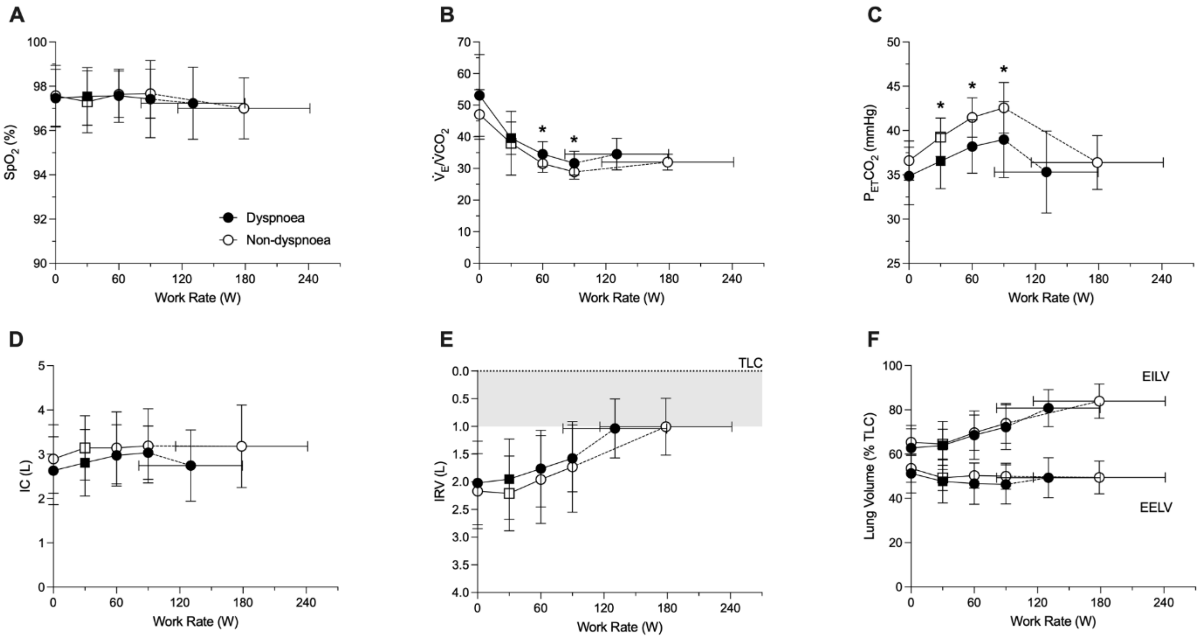

Figure 4. Cardiopulmonary exercise test results comparing gas exchange and non-invasive respiratory mechanical responses between dyspnoea and non-dyspnoea groups.Values are mean±standard deviation, *signifies $P<0.05$ difference between groups following Bonferroni correction for multiple comparisons. Square symbols represent HEWR. Submaximal exercise responses are presented up to 90W achieved by 73% of dyspnoea group and 91% of non-dyspnoea group participants. Abbreviations: EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; HEWR, highest equivalent work rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; PETCO2, partial pressure of end-tidal carbon dioxide; SpO2, oxygen saturation measured by finger pulse oximetry; TLC, total lung capacity; VE/VCO2, ventilatory equivalent for carbon dioxide.

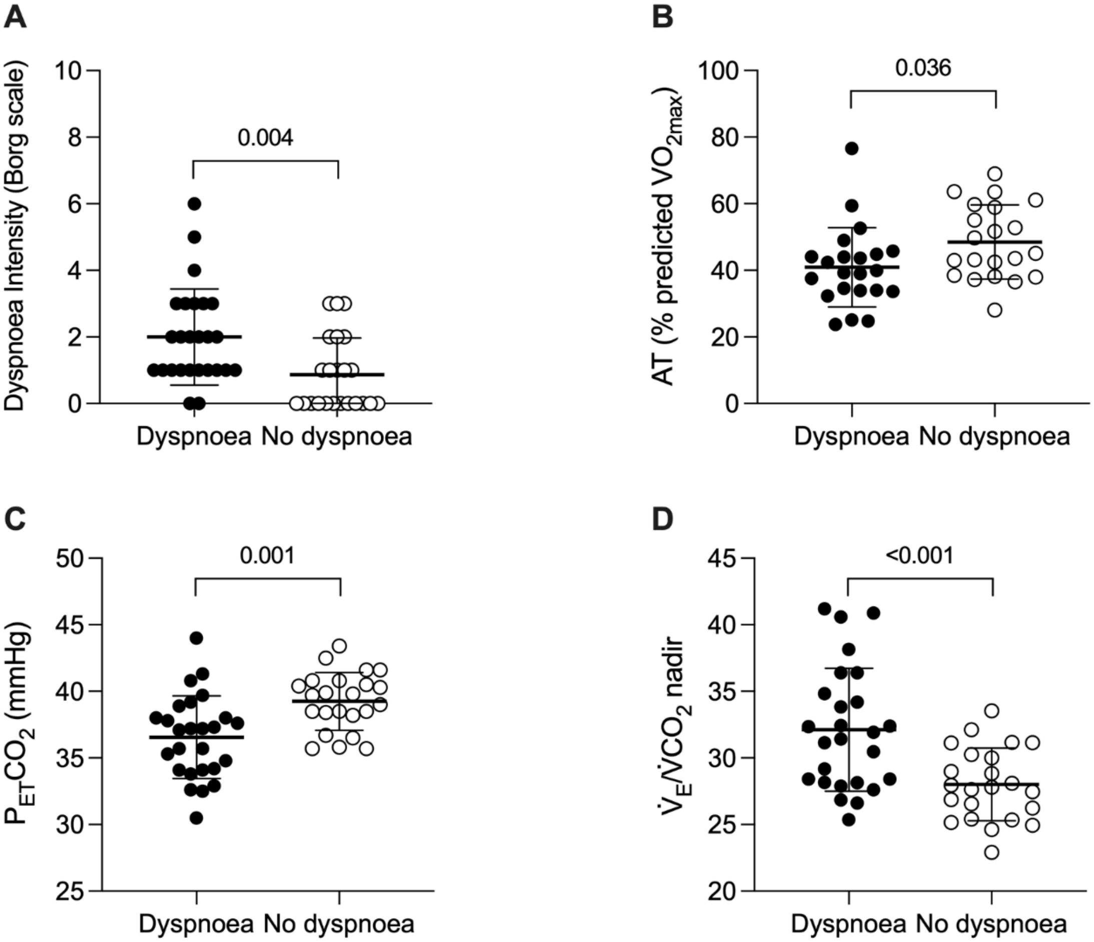

Figure 5. Gas exchange, metabolic and dyspnoea intensity responses for individual participants with and without dyspnoea. Bars represent mean±standard deviation. Dyspnoea intensity and PETCO2 values are presented at HEWR. Abbreviations: AT, anaerobic threshold; HEWR, highest equivalent work rate; PETCO2, partial pressure of end-tidal carbon dioxide; VE/VCO2, ventilatory equivalent for carbon dioxide; VO2max, maximum oxygen uptake.

Exercise responses and mental health symptoms in COVID-19 survivors with dyspnoea

Kathryn M. Milne[1,2], Juthaporn Cowan[3,4,5], Michele R. Schaeffer[1,6], Nha Voduc[3], Vicente Corrales-Medina[4], Kim L. Lavoie[7,8], Julio A. Chirinos[9], Joseph H. Puyat[10], Sara J. Abdallah[4], Jordan A. Guenette[1,2,6]

ONLINE SUPPLEMENT

Supplementary Table 1. Dyspnea descriptor questionnaire.

DESCRIPTORS BREATHLESSNESS

CIRCLE AS MANY (OR AS FEW) OF THE DESCRIPTORS THAT APPLY TO HOW YOUR BREATHING FELT RIGHT AT THE VERY END OF EXERCISE:

1. My breath does not go in all the way
2. Breathing in requires effort
3. I feel that I am suffocating
4. I feel a need for more air
5. My breathing is heavy
6. I cannot take a deep breath in
7. My chest feels tight
8. My breathing requires more work
9. I feel a hunger for more air
10. I feel that my breathing is rapid
11. My breathing feels shallow
12. I feel that I am breathing more air
13. I cannot get enough air in
14. My breath does not go out all the way
15. Breathing out requires more effort

Supplementary Table 2. Multiple regression results for dyspnoea intensity and unpleasantness at highest equivalent work rate.

Independent variable	**Coefficient**	**SE**	***P*-value**
Dyspnoea intensity			
Intercept	-9.913	5.744	0.123
$\dot{V}O_2$ peak, % pred	0.019	0.024	0.441
AT, %$\dot{V}O_2$predmax	-0.020	0.048	0.691
$\dot{V}_E/\dot{V}CO_2$ nadir	0.282	0.120	0.047
D_LCO, % pred	0.039	0.026	0.170
HADS total	-0.023	0.061	0.714
SGRQ total	0.018	0.022	0.455
PSS	-0.166	0.071	0.048
ASI-R	0.019	0.014	0.199
IES-R total	0.426	0.452	0.374
Sex	-0.911	0.770	0.271
Age, years	-0.001	0.030	0.987
Smoking, pack years	-0.073	0.039	0.100
BMI, kg/m^2	0.025	0.044	0.589
Dyspnoea unpleasantness			
Intercept	-9.89	5.615	0.116
$\dot{V}O_2$ peak, % pred	0.003	0.023	0.906
AT, %$\dot{V}O_2$predmax	0.016	0.047	0.747
$\dot{V}_E/\dot{V}CO_2$ nadir	0.305	0.117	0.032
D_LCO, % pred	0.026	0.025	0.339
HADS total	0.009	0.060	0.879
SGRQ total	0.027	0.022	0.259
PSS	-0.096	0.070	0.204
ASI-R	0.012	0.013	0.404
IES-R total	0.142	0.442	0.756
Sex	-0.721	0.753	0.366
Age	-0.023	0.030	0.452
Smoking, pack years	-0.040	0.038	0.322
BMI, kg/m^2	-0.005	0.043	0.915

Abbreviations: ASI-R, Revised Anxiety Sensitivity Index; AT, anaerobic threshold; BMI, body mass index; D_LCO, diffusing capacity of the lungs for carbon monoxide; HADS, Hospital Anxiety and Depression Scale; IES-R, Revised impact of Event Scale; PSS, Perceived Stress Scale; SGRQ, St. George Respiratory Questionnaire; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$, oxygen uptake.