Research paper

Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea

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ABSTRACT

Background: Dyspnea and exercise intolerance are commonly reported post-acute sequelae of SARS-CoV-2 infection (PASC), but routine diagnostic testing is often normal. Cardiopulmonary exercise testing (CPET) offers comprehensive assessment of dyspnea to characterize pulmonary PASC.
Methods: We performed a retrospective cohort study of CPET performed on patients reporting dyspnea and/or exercise intolerance following confirmed Covid-19 between August 1, 2020 and March 1, 2021, and compared them to age- and sex-matched patients with unexplained dyspnea referred for CPET at the same center in the pre-Covid-19 era.
Findings: Compared to matched unexplained dyspnea comparators, PASC patients shared similar medical comorbidities and subjective dyspnea at referral (mMRC score 1.6 ± 0.9 vs. 1.4 ± 0.9, $P = 0.5$). Fifteen (83.3%) PASC patients underwent high resolution computed tomography of the chest, of which half (46.7%) were normal, and 17 (94.4%) patients had pulmonary function testing, of which the majority (76.5%) were normal. All patients underwent CPET, and 12 (67%) had normal findings. Compared to matched comparators, PASC patients had similar peak oxygen consumption, oxygen consumption at ventilatory anaerobic threshold, and ventilatory efficiency measured by the minute ventilation to carbon dioxide production (VE/VCO_2) slope.
Interpretation: Despite prominent dyspnea, physiological abnormalities on CPET were mild across a range of initial Covid-19 severity and similar to matched comparators referred for dyspnea without antecedent SARS-CoV-2.
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1. Introduction

Following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (Covid-19), a substantial proportion of patients describe a heterogenous constellation of persistent symptoms termed post-acute sequelae of SARS-CoV-2 infection (PASC) [1-5]. The exact incidence of PASC is unknown, but it is estimated that approximately 10% of all patients infected with SARS-CoV-2 experience symptoms lasting 1 month, with approximately 2.5% experiencing symptoms lasting beyond 3 months [5]. When applied to over 200 million infections globally, even this relatively low percentage represents a major challenge for the healthcare system [4].

Dyspnea and exercise intolerance are among the most commonly reported symptoms in patients with PASC [1-5], but the underlying physiological abnormalities causing these symptoms are unknown. Routine diagnostics, such as pulmonary function testing (PFT) and high-resolution computed tomography (HRCT) of the chest, are frequently normal in these patients, especially those with mild disease [6,7]. More precise diagnostic tests are therefore necessary to characterize the abnormalities associated with dyspnea and exercise intolerance in PASC. In addition, given the overwhelming scale of the Covid-19 pandemic, it will be important to differentiate symptoms of PASC from dyspnea due to other etiologies which may present coincident with, though not caused by, SARS-CoV-2 infection.

Cardiopulmonary exercise testing (CPET) affords an integrated assessment of cardiopulmonary, pulmonary vascular, systemic

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Research in context

Evidence before this study

Cardiopulmonary exercise testing (CPET) affords an integrated assessment of multiple organ system contributions to exercise limitation and can yield clinically relevant physiological data for patients with multifactorial dyspnea, including survivors of viral pneumonia syndromes like SARS-CoV-2. We searched PubMed for articles since the outbreak of SARS-CoV-2 following January 1, 2020 up to April 13, 2021, using the terms "Cardiopulmonary exercise testing" OR "CPET" OR "Covid-19″ OR "SARS-CoV-2″ and identified 3 cohort studies of patients undergoing CPET at the time of hospital discharge reporting abnormalities inclusive of ventilatory inefficiency, impaired heart rate recovery, and skeletal muscle deconditioning. However, few studies have characterized the results of CPET in patients with long-term persistent symptoms across a range of initial disease severity compared to a matched control population.

Added value of this study

We report comprehensive CPET results of the first 18 post-acute sequelae of SARS-CoV-2 infection patients referred by our institution's Coronavirus Recovery Pulmonary clinic compared to age- and sex-matched comparators with unexplained dyspnea prior to the advent of the Covid-19 pandemic. Despite subjectively prominent dyspnea, physiological abnormalities on CPET were mild across a range of initial Covid-19 severity and were similar to those identified in patients with unexplained dyspnea in the pre-Covid-19 era.

Implications of all the available evidence

Cardiopulmonary exercise testing in patients with post-acute sequelae of SARS-CoV-2 infection reveals mild abnormalities which are similar to those identified in a matched group of dyspneic patients prior to the advent of COVID-19.

vascular, and skeletal muscle contributions to exercise limitation for patients with multifactorial dyspnea, including survivors of respiratory failure and other viral pneumonia syndromes [8-10]. Here, we report the CPET findings in patients with PASC compared to age- and sex-matched patients with unexplained dyspnea prior to the advent of Covid-19.

2. Methods

2.1. Study design

We performed a retrospective cohort study of adult outpatients referred by the Massachusetts General Hospital Coronavirus Recovery Pulmonary Clinic for comprehensive CPET via upright cycle ergometry between August 1, 2020 and March 1, 2021 with antecedent confirmed SARS-CoV-2 infection by nasopharyngeal polymerase chain reaction (PCR) and whose chief complaint was persistent dyspnea and/or exercise intolerance after recovery from acute SARS-CoV-2 infection. Patients referred for CPET who did not have confirmed SARS-CoV-2 infection by PCR were excluded from the PASC cohort. Additionally, patients with a submaximal effort defined by a respiratory exchange ratio (RER) < 1.0 were excluded (*except* PASC case 3 whose RER was 0.98 but had a peak oxygen consumption > 100% predicted). We identified age- and sex-matched comparator patients from a cohort comprised of all patients presenting for CPET

in the same laboratory with a chief complaint of unexplained dyspnea and/or exercise intolerance between January 1, 2019 and January 1, 2020. All patients included in the comparator cohort did not have (1) any positive viral respiratory infection testing in the year prior to their CPET and (2) any mention of a clinical syndrome compatible with viral respiratory infection in the history of present illness documented at the time of their CPET.

The study was approved by the Mass General Brigham's Institutional Review Board (Protocol #2010P001704) and informed consent was obtained from study participants.

2.2. Cardiopulmonary exercise testing and interpretation

Maximal effort CPET was performed on the same cycle ergometer (Lode, the Netherlands) and breath-by-breath gas exchange values were measured by the same metabolic cart (MedGraphics, St. Paul, MN). Data were analyzed according to previously published methods [11-13]. A maximal effort study is defined by a RER > 1.0. We consider a peak oxygen consumption (VO_2) $\geq$ 80% predicted to be normal whereas peak $VO_2 <$ 80% is abnormal. Oxygen pulse is defined as VO_2 divided by heart rate and is equal to the product of stroke volume and arterial-mixed venous blood oxygen content difference (a measure of peripheral oxygen extraction) and is compared to predicted normal values based on age, sex, and height [14]. Ventilatory anaerobic threshold (VAT) was determined by the V-slope method [15], and in all the cases included here, we were able to determine VAT by the V-slope method. Ventilatory efficiency is defined by the minute ventilation to carbon dioxide production (VE/VCO_2) slope which is assessed as the regression slopes of VE versus VCO_2 from the start of exercise to the end of exercise. We additionally analyzed the pre-ventilatory anaerobic threshold (VAT) slope as the regression slope of VE versus VCO2 from the start of exercise to the VAT and the post-VAT slope as the regression slope of VE versus VCO_2 from the VAT to the end of exercise [12].

2.3. Statistical analysis

All continuous variables were reported as median and interquartile range (IQR, 1st-3rd) or mean $\pm$ standard deviation where indicated. Categorical data were reported as numbers and percentages. Continuous variables were analyzed by Student's *t*-test or Mann-Whitney U test according to their distributions based on the results of the Shapiro-Wilk test of normality. Categorical variables were analyzed by Fisher's exact test where appropriate. No adjustment for multiple comparisons was made. No imputation was used for missing data. An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Venn diagrams were created using BioVenn [16].

2.4. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Baseline characteristics of the dyspnea cohorts

A total of 18 patients were included in the PASC and matched comparator cohorts, respectively. Demographics and clinical characteristics for the PASC and comparator patients are summarized in **Table 1**. In the PASC cohort (*n* = 18), the median age was 40.5 (IQR 34−57) and 12 patients (66.7%) were female. The comparator cohort

(n = 18) was matched to the PASC cohort based on age and sex. There were no statistically significant differences in the baseline demographics and comorbidities between the two groups, including baseline cardiopulmonary disease.

In the PASC cohort, 3 (16.7%) patients had pre-existing cardiac disease, 3 (16.7%) patients had pre-existing pulmonary disease, and 6 (33.3%) patients were obese with BMI ≥ 30. In all patients with baseline cardiopulmonary disease, the referring pulmonologists did not feel these diagnoses were sufficient to explain their new respiratory symptoms. The majority (83.3%) were never-smokers, and none were active tobacco smokers. All patients had confirmed SARS-CoV-2 infection by nasopharyngeal PCR. Three (16.7%) patients required hospitalization on a medical ward and 3 (16.7%) were critically ill in the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS); the remainder were managed in the outpatient setting. All patients were referred to the Coronavirus Recovery Pulmonary Clinic with chief complaints of dyspnea and exercise intolerance. The mean modified Medical Research Council (mMRC) Dyspnea Scale score at time of CPET referral was similar between the PASC and matched comparator groups (1.6 ± 0.9 vs. 1.4 ± 0.9, P = 0.5). Fifteen (83.3%) patients underwent HRCT of the chest with prone and expiratory views: 7 (46.7%) were normal, 1 (6.7%) demonstrated isolated mosaicism and air-trapping on expiratory views, 6 (40%) demonstrated residual ground glass opacities, and 1 (6.7%) demonstrated a chronic organizing pneumonia pattern. Seventeen (94.4%) patients had full pulmonary function testing with spirometry, body plethysmography, and measurement of diffusing capacity of the lung for carbon monoxide (D_LCO): 13 (76.5%) were normal, 1 (5.9%) demonstrated combined restriction and impaired D_LCO, and 3 (17.6%) had an isolated impairment in D_LCO. The overlap between normal and abnormal diagnostic studies is provided in **Supplemental Figure 1**.

3.2. Cardiopulmonary exercise testing results in the dyspnea cohorts

All patients underwent CPET on a cycle ergometer and 7 (39%) had concurrent first pass radionuclide ventriculography. CPET variables for the PASC and comparator patients are summarized in **Table 2**. In the PASC cohort, the median duration between index SARS-CoV-2 infection and CPET was 257.5 days (IQR 149−322). Twelve (67%) patients had normal CPET studies. Of the 6 (33%) patients with abnormal studies, 2 (33%) patients had an abnormal cardiovascular response with impaired cardiac output during exercise measured by ventriculography, 2 patients had an early VAT and 4 (67%) patients demonstrated a decreased oxygen pulse. Three of the 4 patients with abnormal oxygen pulse had normal non-invasive indices of cardiac function. One patient with impaired oxygen pulse subsequently underwent invasive CPET with exercise right heart catheterization which confirmed a decreased arterial-to-venous oxygen content difference at peak exercise corroborating impaired peripheral oxygen extraction was the chief exercise limitation.

In the comparator cohort, 12 (66.7%) patients had normal CPET studies. Of the 6 (33.3%) patients with abnormal studies, 1 (16.7%) patient demonstrated a high internal cost of work indicated by a doubling in VO_2 at the onset of unloaded exercise, 2 (33.3%) patients had an abnormal cardiovascular response due to chronotropic incompetence, and 3 (50%) patients had a decreased oxygen pulse, suggesting either impaired stroke volume or decreased arterial mixed-venous oxygen content difference. One of the 3 patients with an impaired oxygen pulse went on to have an invasive CPET which confirmed a decreased arterial-to-venous oxygen content difference at peak exercise secondary to elevated mixed venous oxygen content consistent with impaired peripheral oxygen extraction. None of the patients in this study demonstrated exercise oscillatory ventilation.

3.3. Comparison of physiological variables across dyspnea cohorts

We next compared CPET parameters associated with deficits in specific organ systems across the two cohorts. Patients with PASC

Table 1

Baseline demographics and clinical data for PASC and matched comparator cohorts.

Variable	PASC Cohort (n = 18)	Control Cohort (n = 18)	P-value
Age	40.5 (IQR 34−57)	50.5 (IQR 42−58)	0.34*
Sex (Female)	12 (66.7%)	12 (66.7%)	1.0#
Race			0.2#
White	15 (83.3%)	18 (100%)	
Black	2 (11.1%)	0 (0%)	
Asian	1 (5.6%)	0 (0%)	
Ethnicity			1.0#
Non-Hispanic	17 (94.4%)	16 (88.9%)	
Hispanic	1 (5.6%)	2 (11.1%)	
Language			1.0#
English	17 (94.4%)	18 (100%)	
Spanish	1 (5.6%)	0 (0%)	
Body mass index (BMI)	26.7 (IQR 22.3−34)	29.3 (IQR 21.8−34.3)	0.4*
BMI < 30	12 (66.7%)	10 (55.6%)	
BMI ≥ 30	6 (33.3%)	8 (44.4%)	
Medical comorbidities			
Hypertension	3 (16.7%)	5 (27.8%)	0.4#
Hyperlipidemia	4 (22.2%)	1 (5.6%)	0.3#
Coronary artery disease	2 (11.1%)	1 (5.6%)	1.0#
Atrial fibrillation	0 (0%)	0 (0%)	1.0#
Congestive heart failure	1 (5.6%)	0 (0%)	1.0#
Type 2 diabetes mellitus	1 (5.6%)	0 (0%)	1.0#
Hypothyroidism	2 (11.1%)	1 (5.6%)	1.0#
Depression	4 (22.2%)	1 (5.6%)	0.3#
Anxiety	4 (22.2%)	0 (0%)	0.1#,#
Migraines	5 (28%)	1 (5.6%)	0.07#
COPD	0 (0%)	0 (0%)	1.0#
Asthma	2 (11.1%)	4 (22.2%)	0.7#
Tobacco status			
Never	15 (83.3%)	15 (83.3%)	1.0#
Former	3 (16.7%)	2 (11.1%)	1.0#
Current	0 (0%)	1 (5.6%)	1.0#
Infection Severity			
Outpatient	12 (66.7%)	N/A	N/A
Hospitalized	3 (16.7%)	N/A	N/A
Intensive Care Unit	3 (16.7%)	N/A	N/A
Referring pulmonary symptoms			
Dyspnea	18 (100%)	18 (100%)	1.0#
Exercise intolerance	17 (94%)	2 (11.1%)	P<0.001#
Cough	3 (16.7%)	1 (5.6%)	0.6#
mMRC score	1.6 (range 1−4)	1.4 (range 0−3)	0.5*
HRCT	15 (83.3%)	8 (44.4%)	0.03#
Normal	7 (46.7)	4 (50%)	0.4#
Expiratory mosaicism / air trapping	1 (6.7%)	2 (25%)	1.0#
Ground glass opacities	6 (40%)	1 (12.5%)	0.08#
Fibrosis	0 (0%)	0 (0%)	1.0#
Organizing pneumonia	1 (6.7%)	0 (0%)	1.0#
PFTs	17 (94.4%)	17 (94.4%)	1.0#
Normal	13 (76.5%)	10 (58.8%)	0.5#
Obstruction	0 (0%)	2 (11.8%)	0.5#
Restriction	0 (0%)	1 (5.9%)	1.0#
Restriction + low D_LCO	1 (5.9%)	0 (0%)	1.0#
Isolated low D_LCO	3 (17.6%)	4 (23.5%)	1.0#

PASC, post-acute sequelae of SARS-CoV-2 infection; mMRC, modified Medical Research Council Dyspnea Scale (a patient-reported measure of dyspnea when walking on level ground where 0 = dyspnea only with strenuous exercise, 1 = dyspnea when hurrying or walking up a slight hill, 2 = walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace, 3 = stops for breath after walking 100 yards or after a few minutes, and 4 = too dyspneic to leave house of breathless when dressing); HRCT, high resolution computed tomography; PFTs, pulmonary function tests; D_LCO, diffusing capacity of the lung for carbon monoxide.

* Student's *t*-test.
\# Fisher's exact test.

demonstrated similar resting heart rate (77.5 [IQR 74−84] vs. 73.5 [IQR 62−77.5] beats per minute, $P = 0.05$), peak workload (95 [IQR 76−110] vs. 91 [IQR 64−113]% predicted, $P = 0.4$), peak oxygen consumption (85.5 [IQR 69−100] vs. 85 [IQR 68−100]% predicted, $P = 0.9$), ventilatory anaerobic threshold (VAT) (134.5 [IQR 103−157] vs. 140 [IQR 125−164]% predicted, $P = 0.5$), oxygen pulse (95 [IQR 71−115]% vs. 106 [IQR 102−110]% predicted, $P = 0.3$), and ventilatory efficiency as measured by the minute ventilation to carbon dioxide production (VE/VCO_2) slope (29.8 [IQR 27.4−32.7] vs. 28.4 [IQR 27.2−30.6], $P = 0.15$) (Fig. 1A-E).

We found that the partial pressure of end-tidal CO_2 ($PETCO_2$) at rest and at VAT was similar between the PASC and control groups, and the change in $PETCO_2$ between rest and at VAT was similar between the PASC and control groups (4.8 ± 3.2 vs. 6.2 ± 3.6, $P = 0.2$), suggesting a similar ventilatory response between the PASC and comparator patients. There was no evidence of a primary pulmonary mechanical limitation in either cohort with similar breathing reserve at peak exercise (Fig. 1F). To better understand the observed difference in ventilatory efficiency, we calculated the VE/VCO_2 slope before VAT ($VE/VCO_{2\ pre-VATslope}$), nadir VE/VCO_2 slope ($VE/VCO_{2\ nadir}$), and VE/VCO_2 slope after VAT ($VE/VCO_{2\ post-VATslope}$). The $VE/VCO_{2\ pre-VATslope}$ (Fig. 2A) and the $VE/VCO_{2\ nadir}$ were similar between groups; however, the PASC group demonstrated an increased $VE/VCO_{2\ post-VATslope}$ (34.8 [IQR 32−37] vs. 32 [IQR 28−34], $P = 0.04$) (Fig. 2B).

4. Discussion

We characterized dyspnea and exercise limitation in 18 patients with PASC following confirmed SARS-CoV-2 infection who were referred to a dedicated pulmonary PASC clinic. The majority of patients in our cohort demonstrated normal objective cardiopulmonary testing prior to CPET. The most common abnormalities detected included ground glass opacities on cross-sectional thoracic imaging and impairments in D_LCO. Despite subjectively prominent dyspnea and exercise limitation, physiological abnormalities on CPET were mild across a range of initial Covid-19 severity. The most prominent abnormalities were observed in the two ARDS survivors, both of whom had cardiovascular limitations: one with impaired cardiac output due to chronotropic incompetence and the other with residual cardiomyopathy.

Other investigators have observed that hyperventilation and/or dysregulated ventilatory control could underlie the debilitating cardiorespiratory symptoms in PASC [17]. However, we did not observe a difference in ventilatory efficiency in patients with PASC compared with matched comparators with unexplained dyspnea. Ventilatory efficiency is known to be altered in several cardiorespiratory diseases and may represent either (1) hyperventilation with relatively preserved dead space (normal V_D/V_T), (2) increased V_D/V_T, which results in an exaggerated increase in minute ventilation in response to increasing metabolic demand, or (3) some combination of the two [18,19]. Elevated V_D/V_T leading to decreased ventilatory efficiency is associated with pulmonary vascular disease [20,21], but in our PASC cohort both the VE/VCO_2 slope and the peak VO_2 were in the normal range. In addition, there was normal augmentation of the $PETCO_2$ and no evidence of arterial oxygen desaturation with exercise, all of which argue against substantial pulmonary vascular disease in this cohort [22].

Differences in VE/VCO_2 slope pre- and post-VAT are prognostically meaningful in both cohorts of patients with heart failure with preserved ejection fraction and in an at-risk comparator population [11,12]. Increased early exercise VE/VCO_2 slope or nadir VE/VCO_2 (i.e., during submaximal exercise) is associated with increased cardiovascular risk factors, decreased cardiovascular performance on CPET, and increased death and adverse cardiovascular events [11,12]. In addition, pre-VAT VE/VCO_2 slope and overall VE/VCO_2 slope are potentially sensitive to early exercise hyperventilation [12]. Increased late exercise VE/VCO_2 slope (i.e., during maximal exercise) is associated with decreased cardiovascular risk factors and increased

Table 2
Cardiopulmonary exercise test results in PASC and comparator cohorts.

Variable	PASC Cohort (n = 18)	Control Cohort (n = 18)	P-value
Time between infection and CPET (days)	258 (IQR 149−322)	N/A	N/A
Hemoglobin (gm/dL)	13.9 (IQR 12.5−14.4)	14 (IQR 13.1−14.9)	0.5*
Respiratory exchange ratio (RER)	1.24 (IQR 1.17−1.25)	1.16 (IQR 1.12−1.2)	0.04^
Resting heart rate (bpm)	77.5 (IQR 74−84)	73.5 (IQR 62−77.5)	0.05^
Peak heart rate (bpm)	162 (IQR 142−171)	138 (IQR 132−157)	0.02^
Peak heart rate (% predicted by age)	91 (IQR 82−95)	84 (IQR 69−91)	0.04^
Heart rate recovery at 1 min (bpm)	18.2 ± 8.3	21.2 ± 10	0.4^
Work (Watts)	133 (IQR 123−182)	145 (IQR 76−184)	0.4^
Work (% predicted)	95 (IQR 76−110)	91 (IQR 64−113)	0.4^
Metabolic equivalents (METS)	5.4 (IQR 4.5−8)	5.6 (IQR 4.2−6.8)	1.0^
METS (% predicted)	83.5 (IQR 64−101)	85 (IQR 66−103)	0.9^
Peak oxygen consumption (VO_2)	20 (IQR 16−27)	19.5 (IQR 16−23.5)	0.8^
Peak VO_2 (% predicted)	85.5 (IQR 69−100)	85 (IQR 68−100)	0.9^
Ventilator anaerobic threshold (VAT)	12.4 (IQR 10.5−14.7)	12.9 (IQR 10.3−15.5)	0.8^
VAT (% predicted)	134.5 (IQR 103−157)	140 (IQR 125−164)	0.5^
Oxygen (O_2) pulse	10.15 (IQR 8.3−13.2)	11.65 (IQR 10.1−13.5)	0.5^
O_2 pulse (% predicted)	95 (IQR 71−115)	106 (IQR 102−110)	0.3^
VE/VCO_2 Slope (normal <33)	29.8 (IQR 27.4−32.7)	28.4 (IQR 27.2−30.6)	0.15^
Nadir VE/VCO_2	1.8 (IQR 1.1−3)	2.3 (IQR 1.5−3.5)	0.3^
Pre-VAT VE/VCO_2 Slope	26.6 (IQR 24−29)	25.8 (IQR 24−27)	0.6^
Post-VAT VE/VCO_2 Slope	34.8 (IQR 32−37)	32.0 (IQR 28−34)	0.04^
$PETCO_2$ Rest (mm Hg, normal >36)	34.5 (IQR 32−37)	32 (IQR 32−36)	0.5^
$PETCO_2$ VAT (mm Hg, normal >40)	38 (IQR 36−43)	39 (IQR 37−41)	0.5^
$\Delta PETCO_2$ (mm Hg)	4.8 ± 3.2	6.2 ± 3.6	0.3^
Breathing Reserve (%)	39 (IQR 37−41)	37.5 (IQR 27−54)	0.3^

RER, respiratory exchange ratio (ratio of carbon dioxide produced and oxygen consumed, whereby RER >1.0 indicates a maximum effort study); VO_2, oxygen consumption; MET, metabolic equivalents (one MET = 3.5 ml/kg/min of VO_2, the approximate unit of resting oxygen uptake); VAT, ventilatory anerobic threshold (as determined by the V-slope method); oxygen (O_2) pulse = VO_2/heart rate, the product of stroke volume and arterial-mixed venous blood oxygen content difference; VE/VCO_2 slope, ventilatory efficiency (reflects pulmonary ventilation-perfusion matching and ventilatory drive); PETCO2, partial pressure of end-tidal carbon dioxide (should increase by 3−6 mm Hg from rest to VAT); breathing reserve (difference between estimated maximum voluntary ventilation and minute ventilation achieved).
* Student's t-test.
^ Mann-Whitney U test.

cardiovascular performance and may, in fact, reflect higher physical fitness and better lung function [11]. Our findings of overall normal ventilatory efficiency, similar pre-VAT VE/VCO_2 slope between PASC and non-PASC patients with unexplained dyspnea, similar nadir VE/VCO_2, and increased post-VAT VE/VCO_2 slope in PASC patients all argue against pulmonary vascular disease or a hyperventilatory response to exercise as a distinguishing feature of PASC in our cohort.

The most notable finding in our study is the remarkable similarity of CPET across patients with PASC and those presenting with unexplained dyspnea in the pre-COVID-19 era. Similar cohort studies of
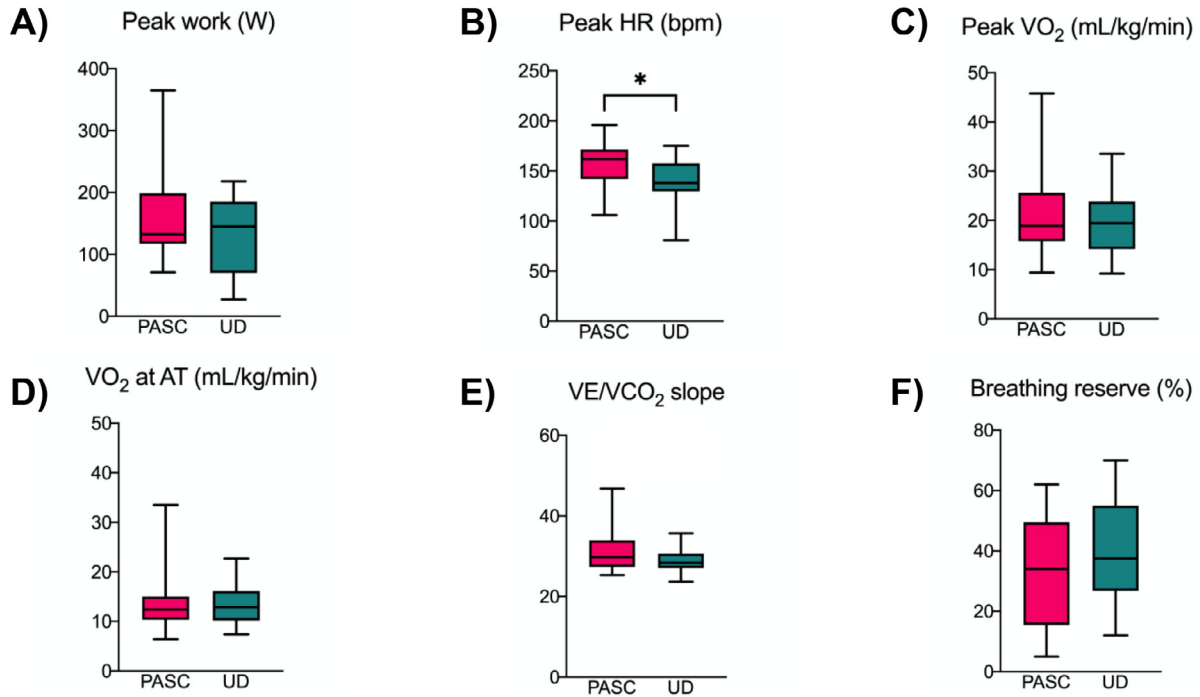
Fig. 1. Patients with PASC have similar exercise performance as non-PASC patients with unexplained dyspnea. Compared to age- and sex-matched comparators with unexplained dyspnea (UD), patients with PASC (post-acute sequelae of SARS-CoV-2 infection) demonstrate (A) similar peak work (W, Watts), (B) increased peak heart rate (HR, beats per minute), (C) similar peak oxygen consumption (VO2, mL/kg/min), (D) similar VO2 at ventilatory anaerobic threshold (VAT), (E) similar minute ventilation to carbon dioxide production (VE/VCO2) slope, and (F) similar breathing reserve (%). Boxes depict the median with interquartile range and whiskers indicate minimum and maximum values. * signifies $P<0.05$.

patients with PASC have evaluated patients within a 3-month time point following initial SARS-CoV-2 infection and have noted abnormalities in peak VO2, ventilatory efficiency, peripheral extraction, and overall conditioning [17,22-24]. In contrast, our cohort was evaluated later in their recovery, with a median of 258 days (range 64 to 62 days) following their index infection. Despite prominent symptoms of persistent dyspnea and exercise intolerance, we find few differences compared to the matched unexplained dyspnea. However, we do observe that the percent predicted for peak workload and metabolic equivalents achieved are at the low end of the normal range. Additionally, we see a greater proportion of PASC patients with an abnormal CPET without baseline cardiopulmonary disease

(**Supplemental Figure 2**), the majority characterized by a decreased O_2 pulse. In those patients in our cohort who had both a decreased oxygen pulse and underwent an additional measure of cardiac function (i.e., ventriculography or invasive CPET), cardiac function was normal, suggestive of a peripheral limitation to exercise as may be seen in impaired skeletal muscle oxygen extraction. We conclude that dyspnea in patients with PASC is due to heterogenous pathophysiology, not all necessarily directly related to antecedent SARS-CoV-2 infection. Importantly, even in patients for whom significant time has elapsed since their index illness, PASC is characterized by significant persistent dyspnea. Careful phenotyping, inclusive of CPET, will be needed in order to appropriately guide treatment.
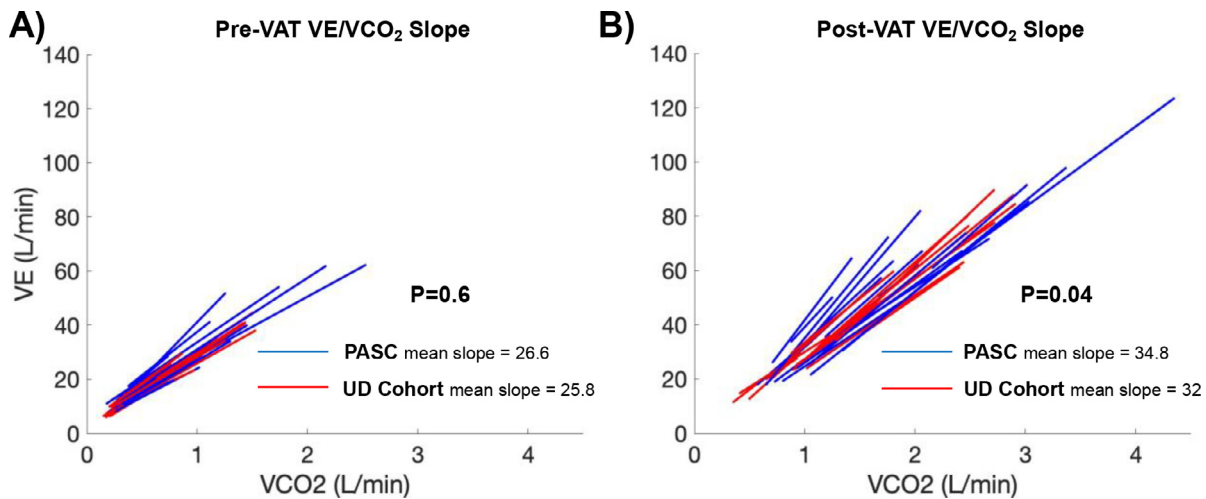

Fig. 2. Patients with PASC demonstrate ventilatory inefficiency post-ventilatory anaerobic threshold. Compared to age- and sex-matched comparators with unexplained dyspnea (UD Cohort), patients with PASC (post-acute sequelae of SARS-CoV-2 infection) demonstrate (A) similar pre-ventilatory anaerobic threshold (VAT) minute ventilation to carbon dioxide production (VE/VCO2) slope (26.6 vs. 25.8, $P = 0.6$) but (B) increased post-VAT VE/VCO2 slope (34.8 vs. 32, $P = 0.04$). VE, minute ventilation (L/min); VCO2, carbon dioxide production (L/min).

There are important limitations to this preliminary prospective study that preclude generalizability. This includes our small sample size, single institution experience, and inherent referral bias. Moreover, communities disproportionately impacted by Covid-19 are not yet fully represented in this sample [25]. It is also possible that CPET findings would be different if testing were conducted closer to the time of Covid-19 diagnosis; however, our patients remained significantly symptomatic at the time of CPET. Nonetheless, given the prevalent impact of PASC, these early reports of cardiopulmonary phenotyping suggest that pulmonary PASC is heterogeneous in nature. We also find that the physiological abnormalities associated with dyspnea and exercise intolerance in the PASC population may be undetectable by standard diagnostic testing. Future studies of dyspnea and exercise limitation in PASC will require more sensitive, non-standard diagnostic testing to fully uncover the underlying pathobiology, including comprehensive CPET.

Declaration of Competing Interest

LPH receives consulting fees from Plaint Therapeutics and Boehringer Ingelheim and serves on the medical advisory board Boehringer Ingelheim, all unrelated to the content of this manuscript. BDM is a data safety monitoring board member for a clinical trial (Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study to Assess Safety and Efficacy of SIR1−365 in Patients with Severe COVID-19) funded by Sironax, USA, unrelated to the content of this manuscript; received payment from Abbvie for providing a presentation on severe COVID-19. GDL serves on the steering committee for clinical trials related to CPET for Amgen, AstraZeneca, Cyclerion, and Cytokinetics, all unrelated to the content of this manuscript; and Cardiopulmonary Exercise Testing Core Laboratory Projects with NHLBI, Amgen, AstraZeneca, Cyclerion, Cytokinetics, Applied Therapeutics, and Abbott, that are not directly related to this work.

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Author contributions

GAA, LCG, DRZ, GDL, and CCH contributed to the concept or design of the study. GAA, DRZ, JNR, AK, CH, and CCH contributed to data acquisition. GAA, DRZ, LCG, GDL, and CCH were involved in the analysis and interpretation of the data. All authors were involved in drafting or critically revising the manuscript, and all authors approved the final version and are accountable for the accuracy and integrity of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. At least three authors (GAA, DRZ, and CCH) have accessed and verified the data).

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Data sharing statement

Individual de-identified patient data have been made available in the Appendix of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101066.

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