Differential cardiopulmonary haemodynamic phenotypes in PASC-related exercise intolerance

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Shareable abstract (@ERSpublications)
The majority of PASC patients exhibit a primary peripheral limitation to exercise. PASC patients with HFpEF exhibited distinct high output heart failure phenotype. There were no reported perioperative complications in these PASC patients. https://bit.ly/4abJ0Pz

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Abstract

Background Post-acute sequelae of COVID-19 (PASC) affect a significant proportion of patients who have previously contracted SARS-CoV-2, with exertional intolerance being a prominent symptom. This study aimed to characterise the invasive haemodynamic abnormalities of PASC-related exertional intolerance using invasive cardiopulmonary exercise testing (iCPET).

Study design and intervention 55 patients were recruited from the Yale Post-COVID-19 Recovery Program, with most experiencing mild acute illness. Supine right heart catheterisation and iCPET were performed on all participants.

Main results The majority (75%) of PASC patients exhibited impaired peak systemic oxygen extraction (pEO_2) during iCPET in conjunction with supranormal cardiac output (CO) (*i.e.*, PASC alone group). On average, the PASC alone group exhibited a "normal" peak exercise capacity, V'_{O_2} (89±18% predicted). ~25% of patients had evidence of central cardiopulmonary pathology (*i.e.*, 12 with resting and exercise heart failure with preserved ejection fraction (HFpEF) and two with exercise pulmonary hypertension (PH)). PASC patients with HFpEF (*i.e.*, PASC HFpEF group) exhibited similarly impaired pEO_2 with well compensated PH (*i.e.*, peak V'_{O_2} and CO >80% respectively) despite aberrant central cardiopulmonary exercise haemodynamics. PASC patients with HFpEF also exhibited increased body mass index of 39 ±7 $kg \cdot m^{-2}$. To examine the relative contribution of obesity to exertional impairment in PASC HFpEF, a control group comprising obese non-PASC group (n=61) derived from a historical iCPET cohort was used. The non-PASC obese patients with preserved peak V'_{O_2} (>80% predicted) exhibited a normal peak pulmonary artery wedge pressure (17±14 *versus* 25±6 mmHg; p=0.03) with similar maximal voluntary ventilation (90±12 *versus* 86±10% predicted; p=0.53) compared to PASC HFpEF patients. Impaired pEO_2 was not significantly different between PASC patients who underwent supervised rehabilitation and those who did not (p=0.19).

Conclusions This study highlights the importance of considering impaired pEO_2 in PASC patients with persistent exertional intolerance unexplained by conventional investigative testing. Results of the current study also highlight the prevalence of a distinct high output HFpEF phenotype in PASC with a primary peripheral limitation to exercise.

Introduction

Since the onset of the COVID-19 pandemic, ~650 million confirmed cases of SARS-CoV-2 infection have been recorded [1]. Estimates of individuals experiencing post-acute sequelae of COVID-19 (PASC) vary but range from 3% to 30% of those having previously contracted COVID-19 [2–4]. While PASC symptoms include multiple organ systems, exertional intolerance in the absence of demonstrable cardiopulmonary pathology is particularly prominent. Despite the prevalence and severity of this symptom, few studies to date have fully characterised the aetiology.

To date, results of conventional cardiopulmonary exercise testing (CPET) have largely been inconclusive, while broad extrapolation of results from invasive CPET (iCPET) studies involving exercise with pulmonary arterial (PA) and radial arterial catheters in place has been limited by small sample size [5, 6]. A study of a small cohort of patients with persistent exercise intolerance a year after mild COVID-19 but no evidence of cardiopulmonary dysfunction by conventional testing demonstrated impaired systemic oxygen (O_2) extraction relative to a control group [6] suggesting a peripheral limitation to exercise. A recent systematic review and meta-analysis study examining CPET performance in patients >3 months after SARS-CoV-2 infection reported that while deconditioning and peripheral limitation to exercise were commonly reported, the current existing literature is limited by inclusion of studies of small sample sizes and varying PASC symptom definitions and CPET interpretations, resulting in increased risk of bias and heterogeneity [7].

Given the prevalence and heterogeneity of PASC, many centres have established post-COVID clinics to provide advanced diagnostics and ongoing support. At our institution, PASC patients with exercise intolerance as the predominant symptom and a non-diagnostic cardiopulmonary workup are often referred for iCPET as a means to explore both peripheral mechanisms and subclinical cardiac comorbidities not readily evident on conventional resting evaluation. The current study was therefore designed to better characterise the invasive haemodynamic aberrancy of PASC-related exertional intolerance using a larger dataset that includes results of both supine right heart catheterisation (RHC) and upright iCPET.

Methods

Data for the study were collected under an IRB-approved protocol (Yale HIC #2000024783) with written informed consent. PASC participants (n=55) were patients referred for iCPET evaluation of persistent exertional intolerance in the setting of either normal conventional investigative testing or if the investigative testing did not explain their persistent exertional intolerance (*i.e.*, unremarkable pulmonary function test, computed tomography chest, noninvasive CPET, cardiac stress testing and echocardiogram). To examine the relative contribution of obesity to the reported exertional intolerance amongst the PASC heart failure with preserved ejection fraction (HFpEF) group, the peak aerobic exercise capacity, maximum voluntary ventilation (MVV) and peak exercise PA wedge pressures of 61 non-PASC obese patients who underwent prior iCPET were compared to the PASC HFpEF patients. At our institution, the iCPET represents a clinically indicated study performed in symptomatic patients only. Following comprehensive evaluation by the Comprehensive Post-Covid Center at Yale (RECOVERY) [8], PASC patients are then referred for iCPET to better understand their persistent unexplained exertional intolerance.

Our methods for resting supine RHC [9, 10] and invasive CPET [6] have been described previously. RHC was performed in the supine position with a five-port pacing PA catheter (Edwards LifeSciences) inserted percutaneously under fluoroscopic and ultrasound guidance into the internal jugular vein and a radial artery catheter concurrently placed in the radial artery. Patients underwent a symptom-limited incremental CPET using an upright cycle ergometer with a breath-by-breath assessment of gas exchange (ULTIMA CPX; Medical Graphics Corporation) along with continuous 12-lead electrocardiography monitoring. Patients underwent 2 min of rest followed by 2 min of unloaded cycling at 40 to 60 rpm. Work rate then was increased continuously using a ramp protocol at 5, 10, 15 or 20 $W \cdot min^{-1}$ depending on the patient's functional status, until peak exercise was achieved as evident either by peak respiratory exchange ratio (RER) of >1.10 or peak heart rate of >85% predicted. Pulmonary and systemic haemodynamics were monitored continuously and simultaneously during exercise (Xper Cardio Physiomonitoring System; Phillips). Pulmonary pressures were recorded at the end of passive exhalation. When respirophasic changes persisted, an electronic average over three respiratory cycles was used. Arterial and mixed venous blood gases and pH were collected during each minute of exercise, and the arterial–mixed venous oxygen content difference was calculated. Systemic oxygen extraction (EO_2) was calculated as arterial oxygen content (C_{aO_2}) minus mixed venous oxygen content (C_{vO_2}) divided by C_{aO_2}. The predicted direct Fick peak cardiac output (CO) is based on the peak predicted exercise capacity (V'_{O_2}) as defined by the Wasserman–Hansen reference equations [11] divided by the assumed arteriovenous content difference. The assumed arteriovenous content difference is 140.7 based on the following equation: 1.34×haemoglobin×($S_{aO_2} - S_{vO_2}$) × correction factor, where S_{aO_2} is the arterial oxygen saturation, S_{vO_2} is the mixed venous oxygen saturation, the haemoglobin is assumed to be 14 $g \cdot dL^{-1}$ and the $S_{aO_2} - S_{vO_2}$ is 0.75 based on the assumption that a normal extraction is 75%. The correction factor is 10.

Direct Fick CO and stroke volume (SV) were determined every minute. Oxygen delivery (D_{O_2}) was calculated by multiplying CO ($mL \cdot kg^{-1} \cdot min^{-1}$) by the C_{aO_2}. Pulmonary vascular resistance was calculated as: mean PA pressure minus PA wedge pressure divided by CO, expressed in Woods units. SV was calculated as CO divided by the heart rate. CO and SV were indexed to body surface area to obtain both

cardiac index and SV index. Physiological dead space was calculated as: $V_D/V_T = (P_{aCO_2} - P_{ETCO_2})/P_{aCO_2}$, where V_D represents dead space volume, V_T is tidal volume, P_{aCO_2} is the PCO_2 in arterial blood and P_{ETCO_2} is the mixed expired P_{aCO_2}.

PA compliance was calculated as the ratio of SV to PA pulse pressure and was expressed as millilitres per millimetre of mercury. Total pulmonary resistance was calculated as the mean PA pressure to CO as expressed in Wood units. To account for the effects of heart rate on the SV, cardiac cycle length was determined by 60/heart rate. The stroke flow was then determined as SV/cardiac cycle length and expressed as mL/s.

Statistical analysis

Unless otherwise stated, values are presented as mean±$_{SD}$. Comparison between peak systemic oxygen extraction (pEO_2) among PASC patients with impaired pEO_2 who underwent a supervised outpatient rehabilitation programme and PASC patients who did not undergo a supervised outpatient rehabilitation programme was performed using an independent t-test. Chi-square tests were used to analyse dichotomous variables. The difference between rest and peak exercise haemodynamics and iCPET data was calculated using an independent t-test. Comparison between the baseline and exercise characteristics of PASC patients with HFpEF and obese non-PASC patients from our historical iCPET cohort were performed using independent t-test. A p-value <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism version 9 software (GraphPad Software), Excel and Tableau.

Results

Of the 55 patients referred for evaluation of post-COVID exercise intolerance, 14 had other pathological factors that could have contributed to symptoms: eight met criteria for HFpEF during supine resting RHC and on subsequent iCPET; two exhibited exercise pulmonary hypertension (ePH) (*i.e.*, mean PA pressure to CO slope >3 with normal ventilation/perfusion scan); and four exhibited exercise HFpEF (*i.e.*, PA wedge pressure to CO slope >2 or peak exercise PA wedge pressure >19 mmHg) [12–14]. In addition to the abnormal mean pulmonary arterial pressure/CO slope, the two ePH patients also exhibited reduced peak exercise aerobic capacity (*i.e.*, peak V'_{O_2} <80% predicted).

The remaining 41 patients had no evidence of a central cardiopulmonary limitation to exercise and were designated as PASC alone. Baseline characteristics of the HFpEF and PASC alone patients are described in table 1 and demonstrate that, on average, patients were well over a year from their acute infection and the majority (n=31,76%) had suffered only mild acute illness [15]. Among the PASC alone group, 26 patients (63%) had undergone supervised physical rehabilitation prior to their iCPET. There was no significant difference between PASC patients with impaired pEO_2 who underwent a supervised rehabilitation programme compared to those who did not undergo a supervised rehabilitation programme (p=0.19).

Table 2 compares variables at rest and peak exercise for PASC alone patients and those with HFpEF and demonstrates both notable similarities and differences. Relative to a previously described control population with a peak EO_2 of 0.78±0.1 [6], both groups exhibited a reduced EO_2 but a preserved peak V'_{O_2} at peak exercise when quantified as the per cent of a predicted value based upon age, height, weight and sex [16]. Both groups exhibited a supranormal peak CO response (119±30% and 132±25% predicted, respectively). The PASC alone group, however, attained a supranormal peak CO response despite low biventricular filling pressures (right atrial pressure (RAP) 3±3 mmHg and pulmonary artery wedge pressure (PAWP) 8±4 mmHg). This response was not simply driven by heart rate, since these patients exhibited appropriate augmentation of their stroke flow (figure 1). Both groups exhibited appropriate decrease in dead space ventilation (V_D/V_T) during exercise (table 2).

Table 3 compares the baseline and exercise characteristics of PASC patients with HFpEF and obese non-PASC cohort derived from our historical iCPET database. There was no difference between the age, sex, body mass index (BMI), peak V'_{O_2} (% predicted) and MVV response between the groups. The peak exercise PAWP was greater in PASC HFpEF compared to obese non-PASC patients.

Discussion

The results indicate that 25% of the patients referred for evaluation of post-COVID exercise intolerance had evidence of an underlying cardiopulmonary disorder that was not apparent on conventional non-investigative testing. Interestingly, the subgroup of patients with HFpEF demonstrated a preserved peak exercise aerobic capacity (peak V'_{O_2} >80% predicted) along with a supranormal peak CO response (132±25% predicted) despite abnormal elevation in left-sided filling pressures in keeping with high-output heart failure. The observed reduction in peak V'_{O_2} relative to peak CO was therefore attributable to the

TABLE 1 Baseline characteristics of PASC alone patients and PASC patients with heart failure with preserved ejection fraction (HFpEF)

Baseline characteristics	PASC alone group	PASC HFpEF group	p-value
Patients n	41	12	
Age years	47±12	53±10	0.13
Sex			
Male	16 (39)	4 (33)	0.53
Female	25 (61)	8 (66)	
Ethnicity			0.52
Hispanic or Latina/o/x	4 (10)	1 (8)	
Not Hispanic or Latina/o/x	34 (83)	10 (71)	
Prefer not to share	3 (7)	1 (8)	
Race			0.10
Black or African American	2 (5)	2 (17)	
White	33 (80)	6 (50)	
Not listed	6 (15)	4 (33)	
BMI kg·m^{-2}	30±5.6	39±7.7	0.0001
Haemoglobin g·dL^{-1}	13.5±1.3	13.3±1.9	0.59
Interval from positive test to iCPET days	462±197	513±189	0.24
Plasma NT-proBNP pg·mL^{-1}	n/a	93 (54–120)	
Pulmonary function test			
FEV_1 %	97±10	86±13	0.01
FVC %	97±14	83±15	0.01
FEV_1/FVC % predicted	100±5	104±9	0.13
D_{LCO} % predicted	97±17	94±16	0.54
Severity of acute SARS-CoV-2 illness			0.23
Mild	31 (76)	5 (35)	
Moderate	7 (17)	3 (21)	
Severe	1 (2)	3 (21)	
Critical	2 (5)	3 (21)	

Data are presented as n (%), mean±SD or median (interquartile range) unless otherwise specified. PASC: post-acute sequelae of COVID-19; BMI: body mass index; iCPET: invasive cardiac pulmonary exercise testing; NT-proBNP: N-terminal pro-B-type natriuretic peptide; FEV_1: forced expiratory volume 1 s; FVC: forced vital capacity; D_{LCO} : diffusing capacity of the lung for carbon monoxide.

impaired pEO_2. In contrast, the only abnormality observed in the remaining 75% of the study population was impaired pEO_2 during iCPET, which occurred in conjunction with supranormal CO and a "normal" (⩾80% predicted) peak V'_{O_2}. Importantly, these distinctions were not evident in a previous iCPET study with a smaller sample size [6].

Peripheral limitation to peak exercise aerobic capacity

One of the main findings of the current study is the demonstration of persistent exertional dyspnoea despite a "normal" peak V'_{O_2} response (*i.e.*, ⩾80% predicted). This finding was similarly reported in a recent study by Ingul *et al.* [17], where the mean peak V'_{O_2} at 3 and 12 months in hospitalised post-COVID-19 patients was preserved during noninvasive CPET. The study by Ingul *et al.*, also reported that despite the interval improvement in peak V'_{O_2} at 12 months, the values of perceived dyspnoea on the BORG CR 10 scale were similar at 3 and 12 months. In the current study, PASC patients alone and those with HFpEF exhibited a disconnect between a "normal" peak V'_{O_2} and a supranormal CO. According to the Fick principle, reduced peak V'_{O_2} can be the result of a blunted CO response (thus decreased D_{O_2} reserve), impaired pEO_2, or both. The observed peak V'_{O_2} that is "greater than predicted levels" in the current study is therefore a reflection of this supranormal CO [5]. However, the subjective exertional capacity of these individuals is reduced and is therefore a function of their impaired pEO_2. Functional implication of impaired pEO_2 is further supported by the elevated peak exercise mixed venous O_2 saturation (MvO_2) of 41.9±9.6% (table 1). While the current study did not have a healthy comparator group, this level of peak MvO_2 is significantly higher than reported for healthy controls (26.5±3.6%) [18]. Thus, in PASC patients undergoing conventional noninvasive CPET, the persistent exertional limitation reported in the setting of a "normal" and even improved peak on noninvasive CPET may in fact reflect an impaired systemic EO_2 [5, 19]. In the current study, using iCPET, we were able to offer a physiological explanation for the

TABLE 2 Invasive cardiopulmonary testing (iCPET) data of PASC alone patients and PASC patients with heart failure with preserved ejection fraction (HFpEF)

	PASC alone group[#]		PASC HFpEF group[¶]	
	Rest	Peak	Rest	Peak
V'_{O_2} mL·min^{-1}	325.6±90.9	1920±781^{+}	325.8±105	1731±436$^{\#\#}$
V'_{O_2} mL min^{-1}·kg^{-1}	3.9±1.1	22.3±6.8^{+}	3.1±0.9§	16.7±2.1$^{f,\#\#}$
V'_{O_2} at AT mL·min^{-1}	1172±510	n/a	1064±320	n/a
V'_{O_2} at AT mL min^{-1}·kg^{-1}	13.72±4.5		10.23±2.0^{f}	
RER	0.89±0.1	1.21±0.08^{+}	0.87±0.1	1.19±0.06$^{\#\#}$
Peak V'_{O_2} % predicted	n/a	89±18	n/a	90±14
V_D/V_T	0.35±0.1	0.38±0.1	0.21±0.1^{+}	0.23±0.1$^{\#\#}$
Heart rate bpm	86±21	156±20^{+}	78±12	137±16$^{\#\#}$
Heart rate % predicted		90±4^{f}		82±9
CO L·min^{-1}	6.5±2.0	17.5±5.3^{+}	6.3±3.9	17.6±2.8$^{\#\#}$
CO % predicted		119±30		132±25
S_{aO_2} %	98±1	98±0.7	98±1	97±3
MvO_2 %	71±5.3	42±9.6^{+}	68±6.7	44±6.8$^{\#\#}$
C_{aO_2} mL·dL^{-1}	18±1.7	19±1.6	18±2.1	18±2.2
C_{vO_2} mL·dL^{-1}	13±1.7	7.9±1.7^{+}	12±1.4	8.1±1.6$^{\#\#}$
Ca-V'_{O_2}	5.1±1.0	11±2.3^{+}	5.3±1.6	10±1.7$^{\#\#}$
D_{O_2} mL kg^{-1}·min^{-1}	15±6.1	40±11$^{+,f}$	11±6.3	30±6.1$^{\#\#}$
EO_2 (Ca-V'_{O_2}/C_{aO_2})	0.27±0.1	0.57±0.1^{+} (0.78± 0.1) [6]	0.29±0.1	0.56±0.1$^{\#\#}$ (0.78±0.1) [6]
CI L min^{-1}·m^{-2}	3.4±1.1	8.8±2.4^{+}	3.3±2.3	8.5±1.1$^{\#\#}$
SVI mL·m^{-2}	38.8±7.3	62.7±33.2^{+}	43.8±30.3	62.7±8.3$^{\#\#}$
RAP mmHg	1±2	3±3^{+}	5±3§	14±6^{f}
mean PAP mmHg	11±4	22±8^{+}	16±4	40±13$^{\#\#,f}$
PAWP mmHg	4±3	8±4	9±3	25±6$^{\#\#,f}$
PAC mL mmHg^{-1}	5.4±2.9	3.1±1.6^{+}	5.4±3.1	2.9±1.2$^{\#\#}$
PVR Wood units	1.31±0.51	0.90±0.47^{+}	1.39±0.95	0.99±0.65$^{\#\#}$

Data are presented as mean±SD unless otherwise specified. Normal mean and standard deviation for EO_2 derived from prior publication [6]. PASC: post-acute sequelae of COVID-19; V'_{O_2}: aerobic exercise capacity; AT: anaerobic threshold; RER: respiratory exchange ratio; V_D: dead space volume; V_T: tidal volume; CO: cardiac output; S_{aO_2}: oxygen saturation in arterial blood; MvO_2: mixed venous oxygen saturation; Ca-V'_{O_2}: difference between arterial and venous oxygen content; C_{aO_2}: oxygen carrying capacity in arterial blood; D_{O_2}: oxygen delivery; EO_2: systemic oxygen extraction; CI: cardiac index; SVI: stroke volume index; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PAC: pulmonary artery compliance; PVR: pulmonary vascular resistance. [#]: n=41; [¶]: n=12; [+]: p<0.05 rest *versus* peak PASC alone group; [§]: p<0.05 rest PASC alone group *versus* rest PASC HFpEF group; [f]: p<0.05 peak PASC alone group *versus* peak PASC HFpEF group; [##]: p<0.05 rest *versus* peak PASC HFpEF group.

ongoing exertional limitation endured by PASC patients who would otherwise demonstrate a "normal" peak V'_{O_2} on conventional noninvasive CPET.

Impaired pEO_2 can be attributable to failure of non-exercising vascular beds to vasoconstrict or direct intramuscular blood flow appropriately, or capillary-to-mitochondrial diffusion inadequacy [5, 6, 20]. Recently, using multi-omic proteomic analysis of mixed venous plasma collected during iCPET, our group demonstrated a persistent inflammatory and endotheliopathy proteomic signature among PASC patients with reduced pEO_2 [21]. While deconditioning is commonly suggested to result in impaired pEO_2, we did not observe a significant difference in pEO_2 amongst PASC patients who underwent a supervised outpatient rehabilitation programme compared to those who did not undergo rehabilitation. Furthermore, the hallmark of deconditioning is reduced peak CO, and bedrest studies demonstrate only a mild impairment of pEO_2 [22]. In contrast, in the current study PASC patients exhibited a high peak exercise CO along with a normal peak heart rate response.

An interesting observation in PASC patients with reduced pEO_2 is the finding of reduced peak exercise RAP (table 1). While these patients had a significant increase in their RAP from rest-to-peak exercise, their peak exercise RAP was reduced compared to previously published normative upright iCPET data [23]. Despite this reduced right-sided filling pressure, however, PASC patients with reduced pEO_2 were able to significantly augment their stroke flow with resultant supranormal peak CO response (figure 1 and table 2).

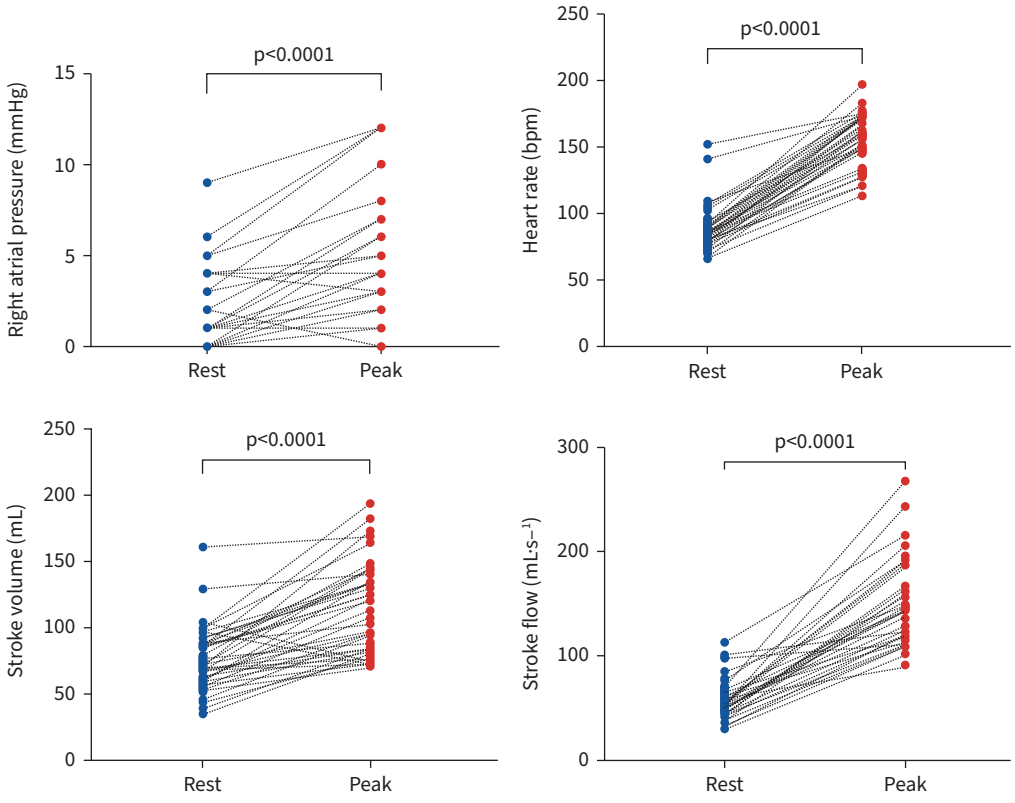

FIGURE 1 Rest to peak change in right atrial pressure, heart rate, stroke volume and stroke flow amongst post-acute sequelae of COVID-19 (PASC) patients with impaired peak systemic oxygen extraction only.

Importantly, this response was not driven by the increasing heart rate, since these patients demonstrated appropriate augmentation in their stroke flow (figure 1). How does a low peak RAP result in a supranormal peak CO response? First, in a normotensive right ventricle (RV), there is no relationship between transmural RAP and either the RV end-diastolic volume or SV [24], such that, a normotensive and compliant RV can either fill at or below its unstressed volume. Therefore, an increased RV end-diastolic volume from increasing right-sided venous return during exercise can occur without a significant change in RV end-diastolic pressure. This phenomenon, along with the low resistance and high capacitance nature of a normal pulmonary circulation (*i.e.*, absence of PH), further allows for the increased stroke flow observed in this PASC cohort.

HFpEF in PASC

Another important finding in the current study is the diagnostic finding of HFpEF amongst PASC patients on supine RHC and iCPET who had otherwise no apparent abnormalities on conventional investigative testing. In contrast to the PASC alone group, PASC patients with HFpEF exhibited a supranormal CO response and a preserved peak V'_{O_2} (table 2). While the exercise haemodynamic finding of impaired pEO_2

TABLE 3 Baseline characteristics of PASC patients with HFpEF and obese non-PASC patients

Variable	PASC HFpEF[#]	Obese non-PASC[¶]	p-value
Age years	53±10	57±3	0.32
Female sex, n (%)	8 (66)	38 (62)	0.77
BMI kg·m^{-2}	39±7	39±18	0.89
MVV % predicted	86±10	90±12	0.53
Peak PAWP mmHg	25±6	17±14	0.03
Peak V'_{O_2} % predicted	90±14	87±36	0.25

Data are presented as mean±SD unless otherwise specified. PASC: post-acute sequelae of COVID-19; HFpEF: heart failure with preserved ejection fraction; BMI: body mass index; MVV: maximum voluntary ventilation; PAWP: pulmonary artery wedge pressure; V'_{O_2}: aerobic exercise capacity. [#]: n=12; [¶]: n=61.

in HFpEF has been previously described [25], the preserved peak V'_{O_2} with supranormal peak CO response represents a distinct pathophysiology phenotype of HFpEF that is in contrast to prior exercise HFpEF reports [13, 26, 27]. It is well established that there exists an inverse relation between N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels and BMI, such that obese individuals (*i.e.*, BMI $\geqslant$30 kg·m^{-2}) [28–30] have much higher odds of having low plasma of NT-proBNP [30]. In our HFpEF cohort the mean BMI was 39 kg·m^{-2}, which likely accounts for the normal NT-proBNP values observed (table 1). Additionally, in a recent large series of consecutive patients, 60% of patients with invasively proven HFpEF had NT-proBNP levels <260 ng·L^{-1} and 37% had levels <125 ng·L^{-1} [31]. In fact, HFpEF patients with normal serum NT-proBNP are more likely to exhibit preserved CO reserve during exercise despite marked elevation in filling pressures [31]. Taken together, these factors are likely to account for the normal reported NT-proBNP in our current HFpEF cohort. Importantly, HFpEF patients with normal NT-proBNP are more likely to exhibit increased risk of death or heart failure readmissions compared with patients without heart failure [31], further emphasising the importance of this particular phenotype.

Another plausible explanation for the reported exertional limitation by our PASC HFpEF cohort is their associated increased BMI (table 1). When compared to a historical cohort of obese non-PASC patients with preserved peak aerobic exercise capacity (peak V'_{O_2} >80% predicted) (table 3), PASC HFpEF patients exhibited an elevated peak PA wedge pressure with similar MVV response (% predicted) arguing against centripetal obesity in itself being a major contributor to exertional limitation in the PASC HFpEF group. However, the high peak PA wedge pressure in the obese non-PASC group (17±14 mmHg) relative to PASC alone (8±4 mmHg) group suggests that obesity may play a role in the abnormal peak PA wedge pressure observed in the PASC HFpEF patients. Previous reports suggest this response is likely attributable to the greater plasma blood volume and epicardial heart volume along with augmented pericardial restraint from increased epicardial adipose tissue deposition [32, 33]. As a result, obese HFpEF patients tend to exhibit greater peak exercise PA wedge pressure response compared to non-obese HFpEF patients, highlighting the influence of elevated BMI on aberrant exercise PA wedge pressure response [32, 33].

While HFpEF and ePH represent a minority of patients in the current cohort, they nonetheless represent an important cause of undifferentiated dyspnoea in the patient population. While there has been little in the way of therapeutic advances to help improve pEO_2 thus far, there have been significant advances in pharmacotherapeutics that has been shown to improve exercise capacity in HFpEF [34] and perhaps ePH [35]. Thus, identifying these particular subgroups of patients is equally as important as physicians caring for PASC patients being able to potentially offer established pharmacotherapy to help improve their patient's symptomatology.

Study limitations

This study has limitations. The current PASC cohort represents a specific phenotype of patients with unremarkable conventional investigative testing who were referred for iCPET and is therefore not representative of the PASC population in general. Similarly, our sample included patients with varying degrees of initial illness and time from initial infection. Further work is needed to characterise PASC with larger sample sizes and at varying points in their recovery trajectory.

Conclusion

Despite these limitations, our study suggests that a large proportion of patients with PASC-associated exertional intolerance exhibit impaired pEO_2, a potentially important consideration for physicians caring for PASC patients with persistent exertional intolerance unexplained by conventional investigative testing. Physicians caring for PASC patients with persistent unexplained exertional intolerance in the setting of conventional investigative testing should also be aware of the diagnostic possibilities of high-output HFpEF and ePH in PASC. While HFpEF and ePH reflect only a minority of patients in the current cohort, helping establish either diagnosis may allow for initiation of established therapies that may help improve patient outcomes [34, 35]. For PASC patients with impaired pEO_2 alone, additional larger studies focused on the underlying molecular basis are needed to characterise these findings and develop therapeutics to address these mechanistic insights.

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