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

Early View

Original research article

Differential Cardiopulmonary Hemodynamic Phenotypes in PASC Related Exercise Intolerance

Peter A. Kahn, Phillip Joseph, Paul M. Heerdt, Inderjit Singh

Please cite this article as: Kahn PA, Joseph P, Heerdt PM, *et al*. Differential Cardiopulmonary Hemodynamic Phenotypes in PASC Related Exercise Intolerance. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00714-2023).

Title: Differential Cardiopulmonary Hemodynamic Phenotypes in PASC Related Exercise Intolerance.

Running title: Cardiopulmonary Hemodynamic Phenotypes in PASC.

Author Names:
Peter A. Kahn MD MPH[1]
Phillip Joseph, MD[1]
Paul M. Heerdt, MD PhD[2]
Inderjit Singh, MD[1]

Author Affiliations:
1) Yale School of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine
2) Department of Anesthesiology, Division of Applied Hemodynamics, Yale New Haven Hospital and Yale School of Medicine

Corresponding Author:
Inderjit Singh MD FRCP FCCP
15 York Street
LLCI 106
PO Box 208057
New Haven 06520-8057
Tel: 203-785-4196
Inderjit.singh@yale.edu

Word Count: 2969 words

Keywords: PASC, invasive CPET, iCPET, Long-COVID.

Author contributions: IS, PAK, PMH, PJ all had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. IS and PAK contributed the study design, data analysis and interpretation, and the writing of the manuscript. PMH and PJ contributed to data interpretation and the writing of the manuscript.

Financial and non-financial disclosures: none

Conflict of interest: no conflict exists for all the authors.

Funding: none

Take home message: 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.

Abstract:

Background: Post-acute sequelae of COVID-19 (PASC) affects a significant portion of patients who have previously contracted SARS-CoV-2, with exertional intolerance being a prominent symptom. **Study Objective:** This study aimed to characterize the invasive hemodynamic abnormalities of PASC-related exertional intolerance using a larger data set from invasive cardiopulmonary exercise testing (iCPET). **Study Design & Intervention:** Fifty-five patients were recruited from the Yale Post-COVID-19-Recovery-Program, with most experiencing mild acute illness. Supine right heart catheterization (RHC) 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, VO_2 (89±18% predicted). Approximately 25% of patients had evidence of central cardiopulmonary pathology (i.e., 12 with resting and exercise HFpEF and 2 with exercise PH). PASC patient with HFpEF (i.e., PASC HFpEF group) exhibited similarly impaired pEO_2 with well compensated PH (i.e., peak VO_2 and cardiac output >80% respectively) despite aberrant central cardiopulmonary exercise hemodynamics. PASC patients with HFpEF also exhibited increased body mass index of 39±7 kg/m^2. To examine the relative contribution of obesity to exertional impairment in PASC HFpEF, a control group compromising of obese non-PASC group (n=61) derived from historical iCPET cohort was used. The non-PASC obese patients with preserved peak VO_2 (>80% predicted) exhibited a normal peak pulmonary artery wedge pressure (17±14 vs. 25±6 mmHg; p=0.03) with similar maximal voluntary ventilation (90±12 vs. 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 current study also highlights the prevalence of a distinct high output failure HFpEF phenotype in PASC with a primary peripheral limitation to exercise.

Abstract word count: 240 words.

Introduction:

Since the onset of the COVID-19 pandemic, approximately 650 million confirmed cases of SARS-CoV-2 infection have been recorded[1]. Estimates of individuals experiencing 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 characterized the etiology.

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[7] suggesting a peripheral limitation to exercise. A recent systematic review and meta-analysis study examining CPET performance in patients more than 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, varying PASC symptom definitions and CPET interpretations, resulting in increased risk of bias and heterogeneity[8].

Given the prevalence and heterogeneity of PASC, many centers 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 characterize the invasive hemodynamic aberrancy of PASC-related exertional intolerance using a larger dataset that includes results of both supine right heart catheterization (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, acute computed tomography chest, non-invasive CPET, cardiac stress testing, and echocardiogram). To examine the relative contribution of obesity to the reported exertional intolerance amongst the PASC 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)[9], PASC patients are then referred for iCPET to better understand their persistent unexplained exertional intolerance.

Our method for resting supine RHC[10,11] 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 revolutions per minute. Work rate then was increased continuously using a ramp protocol at 5, 10, 15, or 20 W/min 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 hemodynamics 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 (CaO_2) minus mixed venous oxygen content (CvO_2) divided by CaO_2. The predicted

direct Fick peak cardiac output is based on the peak predicted VO_2 as defined by the Wasserman-Hansen reference equations[12] divided by the assumed arterio-venous (AV) content difference. The assumed A-V content difference is 140.7 based on the following equation: 1.34 × Hemoglobin × (SaO_2-SvO_2) × correction factor, where the hemoglobin is assumed to be 14 g/dL and the SaO_2-SvO_2 is 0.75 based on the assumption that a normal extraction is 75%. The correction factor is 10.

Direct Fick cardiac output and stroke volume were determined every minute. Oxygen delivery (DO_2) was calculated by multiplying cardiac output by the CaO_2. Pulmonary vascular resistance was calculated as: mean PA pressure minus PA wedge pressure divided by cardiac output, expressed in Woods units. Stroke volume (SV) was calculated as cardiac output (CO) divided by the heart rate. CO and SV were indexed to body surface area to obtain both cardiac index and SV index. Physiologic dead space was calculated as: $VD/VT = (PaCO_2 – PETCO_2) / PaCO_2$, where VD represents dead space volume, VT is tidal volume, $PaCO_2$ is the PCO_2 in arterial blood, and $PETCO_2$ is the mixed expired PCO_2.

PA compliance was calculated as the ratio of SV to PA pulse pressure and was expressed as milliliters per millimeter of mercury. Total pulmonary resistance (TPR) was calculated as the mean PA pressure to CO as expressed in Woods units. To account for the effects of heart rate on the stroke volume (SV), cardiac cycle length was determined as the 1000 / heart rate and expressed as milliseconds per beat (ms/beat). The stroke flow was then determined as SV / cardiac cycle length and expressed as mL/(ms/beat).

Statistical Analysis:

Unless otherwise stated, values are presented as mean (standard deviation). Comparison between pEO_2 among PASC patients with impaired pEO_2 who underwent supervised out-patient rehabilitation program and PASC patients did not undergo supervised out-patient rehabilitation program was performed using an independent t test. Chi-square tests were used to analyze dichotomous variables. The difference between rest and peak exercise hemodynamics and iCPET data were performed 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 pathologic factors that could have contributed to symptoms: 8 met criteria for heart failure with preserved ejection fraction (HFpEF) during *supine* resting RHC and on subsequent iCPET; 2 exhibited exercise pulmonary hypertension (ePH) (i.e., mean PA pressure to cardiac output slope >3 with normal ventilation/perfusion scan; and 4 exhibited exercise HFpEF (i.e., PA wedge pressure to cardiac output slope >2 or peak

exercise PA wedge pressure >19 mmHg)[13-15]. In addition to the abnormal mPAP/CO slope, the 2 ePH patients also exhibited reduced peak exercise aerobic capacity (i.e., peak VO_2 <80% predicted).

The remaining 41 patients had no evidence of a potential 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[16]. Among the PASC alone group, 26 patients (63%) underwent supervised physical rehabilitation prior to their iCPET. There was no significant difference between PASC patients with impaired pEO_2 who underwent supervised rehabilitation program compared to those who did not undergo supervised rehabilitation program (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 VO_2 at peak exercise when quantified as the percent of a predicted value based upon age, height, weight, and gender[17]. Both groups exhibited a supranormal peak cardiac output (CO) response (119±30% and 132±25% predicted, respectively). The PASC alone group however, attained a supra-normal peak CO response despite low cardiac filling pressures (RAP 3±3 and 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 (VD/VT) 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 VO_2 (% predicted), and MVV response between the groups. The peak exercise PA wedge pressure between was greater in PASC HFpEF compared to obese non-PASC patients.

Discussion:

Results indicate that 25% of the patients referred for evaluation of post-COVID exercise intolerance had evidence of pre-existing cardiopulmonary that was not apparent on conventional non-investigative testing. Interestingly, the subgroup of patients with HFpEF demonstrated a preserved peak exercise aerobic capacity (peak VO_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 VO_2 relative to peak CO was therefore attributable to the impaired pEO_2. In contrast, the only abnormality observed in the remaining 75% of the study population was impaired pEO_2 during iCPET, that occurred in conjunction with supra-normal CO and a "normal" (≥80% predicted) peak VO_2. Importantly, these distinctions were not evident in a previous iCPET study with a smaller sample size[7].

Peripheral Limitation to Peak Exercise Aerobic Capacity

One of the main findings of the current study is the demonstration of persistent exertional dyspnea despite a “normal” peak VO_2 response (i.e., ≥80% predicted). This finding was similarly reported in a recent study by *Ingul et al.,* where the average peak VO_2 at 3- and 12-months in hospitalized post-COVID-19 patients was preserved during non-invasive CPET. The study by *Ingul et al.,* also reported that despite the interval improvement in peak VO_2 at 12 months, the values of perceived dyspnea on BORG CR 10 scale were similar at 3- and 12-months[18]. In the current study, PASC patients alone and those with HFpEF exhibited a disconnect between a “normal” peak VO_2 and a supra-normal CO. According to the Fick principle, reduced peak VO_2 can be the result of a blunted CO response (thus decreased DO_2 reserve), impaired pEO_2, or both. The observed peak VO_2 that is “greater than predicted levels” in the current is therefore a reflection of this supra-normal 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%)[19]. Thus, in PASC patients undergoing conventional non-invasive CPET, the persistent exertional limitation reported in the setting of a “normal” and even improved peak VO_2 on non-invasive CPET may in fact reflect an impaired systemic EO_2.[20,21]. In the current study, using iCPET, we were able to offer a physiological explanation for the ongoing exertional limitation endured by PASC patients who would otherwise demonstrate a “normal” peak VO_2 on conventional non-invasive 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 [7,20,22]. 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[23]. 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 supervised out-patient rehabilitation program 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[24]. 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 right atrial pressure (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[25]. Despite this reduced right sided filling pressures 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).** 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 RV, there is no relationship between transmural RAp and either the RV end-diastolic volume or SV[26], such that, a normotensive and

compliant RV can either fill at or below its unstressed volume. Therefore, an increase 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 their pulmonary circulation (i.e., absence of PH) further allows for the increased stroke flow observed in this PASC cohort.

Heart Failure with Preserved Ejection Fraction 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 high output heart failure phenotype with a supra-normal CO response and a preserved peak VO_2 **(Table 2).** While the exercise hemodynamic finding of impaired pEO_2 in HFpEF has been previously described[27], the preserved peak VO_2 with supra-normal peak CO response represents a distinct pathophysiology phenotype of HFpEF that is in contrast to prior exercise HFpEF reports[14,28,29]. It is well established that there exists an inverse relation between N-terminal prohormone brain natriuretic peptide (NT-pro-BNP) levels and body mass index (BMI), such that obese individuals (i.e., BMI≥ 30 kg/m^2)[30-32] have much higher odds of having low plasma of NT-pro-BNP[32]. In our HFpEF cohort the average BMI was 39 kg/m^2 which likely accounts for the normal NT-pro-BNP values observed (**Table 1**). Additionally, in a recent large series of consecutive patients, 60% of patients with invasively proven HFpEF had NT-pro-BNP levels <260 ng/L and 37% had levels <125 ng/L[33]. In fact, HFpEF patients with normal serum NT-pro-BNP are more likely to exhibit

preserved cardiac output reserve during exercise despite marked elevation in filling pressures[33]. Taken together, these factors are likely to account for the normal reported NT-pro-BNP in our current HFpEF cohort. Importantly, HFpEF patients with normal NT-pro-BNP are more likely to exhibit increased risk of death or heart failure readmissions compared with patients without heart failure[33], further emphasizing 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 VO_2 >80% predicted) **(Table 3)**, PASC HFpEF patients exhibited an elevated peak PA wedge pressure with similar MVV response (%predicted) arguing against 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[34,35]. 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 body mass index on aberrant exercise PA wedge pressure response[34,35].

While HFpEF and ePH represent a minority of patients in the current cohort, they nonetheless represent an important cause of undifferentiated dyspnea in the patient

population. While there has been little therapeutic advances to help improve pEO_2 thus far, there has been significant advances in pharmacotherapeutics to help improve outcomes in HFpEF[36] and ePH[37]. Thus, identifying these particular subgroups of patients are equally as important as physicians caring for PASC patients are able to 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 characterize PASC with larger sample sizes and at varying points in their recovery trajectory.

Conclusion

Despite these limitations, our study suggests that a large portion 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 by 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 allows for initiation of established

therapies that may help improve patient outcomes[36,37]. For PASC patients with impaired pEO_2 alone, additional larger studies focused on the underlying molecular basis are needed to characterize these findings and develop therapeutics to address these mechanistic insights.

Table 1

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

Baseline Characteristics	PASC alone group (n=41)	PASC HFpEF group (n=12)	p-value
Age, years	47 (12)	53 (10)	0.13
Gender, N (%)			
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
Hemoglobin (g/dL)	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-pro-BNP (pg/mL)	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
DLCO	97 (17)	94 (16)	0.54
Severity of acute SARS-CoV-2 illness, N (%)			0.23

Mild	31 (76)	5 (35)	
Moderate	7 (17)	3 (21)	
Severe	1 (2)	3 (21)	
Critical	2 (5)	3 (21)	

Data presented as mean and (standard deviation) or median (interquartile range) unless otherwise specified. BMI – body mass index; iCPET – invasive cardiac pulmonary exercise testing. NT-pro-BNP – N-terminal Pro-B-Type Natriuretic Peptide; FEV – forced expiratory volume in one second; FVC – forced vital capacity; DLCO – diffusing capacity of lung for carbon monoxide.

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 (n=41)		PASC HFpEF group (n=12)	
	Rest	**Peak**	**Rest**	**Peak**
VO_2 (mL/min)	325.6 (90.9)	1920 (781)[c]	325.8 (105)	1731 (436)[d]
VO_2 (mL/min/kg)	3.9 (1.1)	22.3 (6.8)[c]	3.1 (0.9)[a]	16.7 (2.1)[bd]
VO_2 at AT (mL/min)	1172 (510)	n/a	1064 (320)	n/a
VO_2 at AT (mL/min/kg)	13.72 (4.5)		10.23 (2.0)[b]	
RER	0.89 (0.1)	1.21 (0.08)[c]	0.87 (0.1)	1.19 (0.06)[d]
Peak VO_2 (%predicted)	n/a	89 (18)	n/a	90 (14)
VD /VT	0.35 (0.1)	0.38 (0.1)	0.21 (0.1)[c]	0.23 (0.1)[d]
Heart rate (bpm) **Heart rate (% predicted)**	86 (21)	156 (20)[c] 90 (4)[b]	78 (12)	137 (16)[d] 82 (9)
CO (L/min) **CO (% predicted)**	6.5 (2.0)	17.5 (5.3)[c] 119 (30)	6.3 (3.9)	17.6 (2.8)[d] 132 (25)
SaO_2 (%)	98 (1)	98 (0.7)	98 (1)	97 (3)
MvO2 (%)	71 (5.3)	42 (9.6)[c]	68 (6.7)	44 (6.8)[d]
CaO_2 (mL/dL)	18 (1.7)	19 (1.6)	18 (2.1)	18 (2.2)
CvO_2 (mL/dL)	13 (1.7)	7.9 (1.7)[c]	12 (1.4)	8.1 (1.6)[d]
Ca-vO_2	5.1 (1.0)	11 (2.3)[c]	5.3 (1.6)	10 (1.7)[d]
DO_2 (mL/kg/min)	15 (6.1)	40 (11)[cb]	11 (6.3)	30 (6.1)[d]
EO_2 (Ca-vO_2 / CaO_2)	0.27 (0.1)	0.57 (0.1)[c] [0.78 (0.1)][6]	0.29 (0.1)	0.56 (0.1)[d] [0.78 (0.1)][6]

CI (L/min/m^2)	3.4 (1.1)	8.8 (2.4)[c]		3.3 (2.3)	8.5 (1.1)[d]
SVI (mL/m^2)	38.8 (7.3)	62.7 (33.2)[c]		43.8 (30.3)	62.7 (8.3)[d]
RAP (mmHg)	1 (2)	3 (3)[c]		5 (3)[a]	14 (6)[b]
mean PAP (mmHg)	11 (4)	22 (8)[c]		16 (4)	40 (13)[db]
PAWP (mmHg)	4 (3)	8 (4)		9 (3)	25 (6)[db]
PAc (mL/mmHg)	5.4 (2.9)	3.1 (1.6)[c]		5.4 (3.1)	2.9 (1.2)[d]
PVR (Wood Units)	1.31 (0.51)	0.90 (0.47)[c]		1.39 (0.95)	0.99 (0.65)[d]

Data presented as mean and (standard deviation) unless otherwise specified. Normal mean and standard deviation for EO_2 derived from prior publication[6]. AT – anerobic threshold; RER – respiratory exchange ratio; CO – cardiac output; VO_2 – aerobic exercise capacity; SaO_2 – oxygen saturation in arterial blood; MvO_2 – mixed venous oxygen saturation; DO_2 – oxygen delivery; CaO_2 – oxygen carrying capacity in arterial blood: 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.

[a]p<0.05 rest PASC alone group vs. rest PASC HFpEF group

[b]p<0.05 peak PASC alone group vs. peak PASC HFpEF group

[c]p<0.05 rest vs. peak PASC alone group

[d]p<0.05 rest vs. peak PASC HFpEF group

.

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

Variable	PASC HFpEF (n=12)	Obese non-PASC (n=61)	p-value
Age	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 VO_2 (% predicted)	90 (14)	87 (36)	0.25

Data presented as mean and (standard deviation) unless otherwise specified. BMI – body mass index; MVV – maximum voluntary ventilation; PAWp – pulmonary artery wedge pressure; VO_2 – aerobic exercise capacity.

References

1. WHO. WHO Coronavirus (COVID-19) Dashboard. 2022; https://covid19.who.int/. Accessed 8 December, 2022.
2. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, Lekoubou A, Oh JS, Ericson JE, Ssentongo P, Chinchilli VM. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Netw Open.* 2021;4(10):e2128568.
3. Global Burden of Disease Long CC, Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, Blyuss O, Bobkova P, Bonsel G, Borzakova S, Buonsenso D, Butnaru D, Carter A, Chu H, De Rose C, Diab MM, Ekbom E, El Tantawi M, Fomin V, Frithiof R, Gamirova A, Glybochko PV, Haagsma JA, Haghjooy Javanmard S, Hamilton EB, Harris G, Heijenbrok-Kal MH, Helbok R, Hellemons ME, Hillus D, Huijts SM, Hultstrom M, Jassat W, Kurth F, Larsson IM, Lipcsey M, Liu C, Loflin CD, Malinovschi A, Mao W, Mazankova L, McCulloch D, Menges D, Mohammadifard N, Munblit D, Nekliudov NA, Ogbuoji O, Osmanov IM, Penalvo JL, Petersen MS, Puhan MA, Rahman M, Rass V, Reinig N, Ribbers GM, Ricchiuto A, Rubertsson S, Samitova E, Sarrafzadegan N, Shikhaleva A, Simpson KE, Sinatti D, Soriano JB, Spiridonova E, Steinbeis F, Svistunov AA, Valentini P, van de Water BJ, van den Berg-Emons R, Wallin E, Witzenrath M, Wu Y, Xu H, Zoller T, Adolph C, Albright J, Amlag JO, Aravkin AY, Bang-Jensen BL, Bisignano C, Castellano R, Castro E, Chakrabarti S, Collins JK, Dai X, Daoud F, Dapper C, Deen A, Duncan BB, Erickson M, Ewald SB, Ferrari AJ, Flaxman AD, Fullman N, Gamkrelidze A, Giles JR, Guo G, Hay SI, He J, Helak M, Hulland EN, Kereselidze M, Krohn KJ, Lazzar-Atwood A, Lindstrom A, Lozano R, Malta DC, Mansson J, Mantilla Herrera AM, Mokdad AH, Monasta L, Nomura S, Pasovic M, Pigott DM, Reiner RC, Jr., Reinke G, Ribeiro ALP, Santomauro DF, Sholokhov A, Spurlock EE, Walcott R, Walker A, Wiysonge CS, Zheng P, Bettger JP, Murray CJL, Vos T. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA : the journal of the American Medical Association.* 2022;328(16):1604-1615.
4. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* 2023.
5. Singh I, Joseph P. Short and Long Term Non-Invasive Cardiopulmonary Exercise Assessment in previously Hospitalized COVID-19 Patients. *Eur Respir J.* 2022.

6. Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. *Chest.* 2022;161(1):54-63.
7. Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. *Chest.* 2021.
8. Durstenfeld MS, Sun K, Tahir P, Peluso MJ, Deeks SG, Aras MA, Grandis DJ, Long CS, Beatty A, Hsue PY. Use of Cardiopulmonary Exercise Testing to Evaluate Long COVID-19 Symptoms in Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2022;5(10):e2236057.
9. Lutchmansingh DD, Knauert MP, Antin-Ozerkis DE, Chupp G, Cohn L, Dela Cruz CS, Ferrante LE, Herzog EL, Koff J, Rochester CL, Ryu C, Singh I, Tickoo M, Winks V, Gulati M, Possick JD. A Clinic Blueprint for Post-Coronavirus Disease 2019 RECOVERY: Learning From the Past, Looking to the Future. *Chest.* 2020.
10. Joseph P, Savarimuthu S, Zhao J, Yan X, Oakland HT, Cullinan M, Heerdt PM, Singh I. Noninvasive determinants of pulmonary hypertension in interstitial lung disease. *Pulm Circ.* 2023;13(1):e12197.
11. Oakland HT, Joseph P, Elassal A, Cullinan M, Heerdt PM, Singh I. Diagnostic utility of sub-maximum cardiopulmonary exercise testing in the ambulatory setting for heart failure with preserved ejection fraction. *Pulm Circ.* 2020;10(4):2045894020972273.
12. Wasserman K, Ovid Technologies Inc. Principles of exercise testing and interpretation. In: 5th ed. S.l.: Lippincott Williams & Wilkins,; 2011: https://yale.idm.oclc.org/login?URL=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=booktext&NEWS=N&DF=bookdb&AN=01439422/5th_Edition&XPATH=/PG(0).
13. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Radegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, Group EESD. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *The European respiratory journal.* 2023;61(1).
14. Singh I, Rahaghi FN, Naeije R, Oliveira RKF, Systrom DM, Waxman AB. Right Ventricular-Arterial Uncoupling During Exercise in Heart Failure With Preserved Ejection Fraction: Role of Pulmonary Vascular Dysfunction. *Chest.* 2019.
15. Oliveira RK, Agarwal M, Tracy JA, Karin AL, Opotowsky AR, Waxman AB, Systrom DM. Age-related upper limits of normal for maximum upright exercise pulmonary haemodynamics. *Eur Respir J.* 2016;47(4):1179-1188.
16. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med.* 2020;383(18):1757-1766.
17. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2003;167(2):211-277.
18. Skjorten I, Ankerstjerne OAW, Trebinjac D, Bronstad E, Rasch-Halvorsen O, Einvik G, Lerum TV, Stavem K, Anne E, Ingul CB. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J.* 2021.

19. Mourtzakis M, Gonzalez-Alonso J, Graham TE, Saltin B. Hemodynamics and O2 uptake during maximal knee extensor exercise in untrained and trained human quadriceps muscle: effects of hyperoxia. *J Appl Physiol (1985).* 2004;97(5):1796-1802.
20. Singh I, Joseph P. Short- and long-term noninvasive cardiopulmonary exercise assessment in previously hospitalised COVID-19 patients. *Eur Respir J.* 2023;61(2).
21. Naeije R, Caravita S. Phenotyping long COVID. *Eur Respir J.* 2021;58(2).
22. Heerdt PM, Shelley B, Singh I. Impaired systemic oxygen extraction long after mild COVID-19: potential perioperative implications. *Br J Anaesth.* 2022;128(3):e246-e249.
23. Singh I, Leitner BP, Wang Y, Zhang H, Joseph P, Lutchmansingh DD, Gulati M, Possick JD, Damsky W, Hwa J, Heerdt PM, Chun HJ. Proteomic profiling demonstrates inflammatory and endotheliopathy signatures associated with impaired cardiopulmonary exercise hemodynamic profile in Post Acute Sequelae of SARS-CoV-2 infection (PASC) syndrome. *Pulm Circ.* 2023;13(2):e12220.
24. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation.* 1968;38(5 Suppl):VII1-78.
25. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ.* 2016;6(1):55-62.
26. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ. The relationship between pericardial pressure and right atrial pressure: an intraoperative study. *Circulation.* 1986;73(3):428-432.
27. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail.* 2015;8(2):286-294.
28. Singh I, Oliveira RKF, Naeije R, Rahaghi FN, Oldham W, Systrom DM, Waxman AB. Pulmonary Vascular Distensibility and Early Pulmonary Vascular Remodeling in Pulmonary Hypertension. *Chest.* 2019.
29. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J.* 2016;37(43):3293-3302.
30. McCord J, Mundy BJ, Hudson MP, Maisel AS, Hollander JE, Abraham WT, Steg PG, Omland T, Knudsen CW, Sandberg KR, McCullough PA, Breathing Not Properly Multinational Study I. Relationship between obesity and B-type natriuretic peptide levels. *Arch Intern Med.* 2004;164(20):2247-2252.
31. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Maisel AS. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J.* 2006;151(5):999-1005.
32. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation.* 2004;109(5):594-600.

33. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J.* 2022;43(20):1941-1951.
34. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail.* 2020;8(8):657-666.
35. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. *Circulation.* 2017;136(1):6-19.
36. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S, Sharma K, Khan SS, Chandra L, Gordon RA, Ryan JJ, Chaudhry SP, Joseph SM, Chow CH, Kanwar MK, Pursley M, Siraj ES, Lewis GD, Clemson BS, Fong M, Kosiborod MN. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med.* 2021;27(11):1954-1960.
37. Segrera SA, Lawler L, Opotowsky AR, Systrom D, Waxman AB. Open label study of ambrisentan in patients with exercise pulmonary hypertension. *Pulm Circ.* 2017;7(2):531-538.

Figure legend:

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

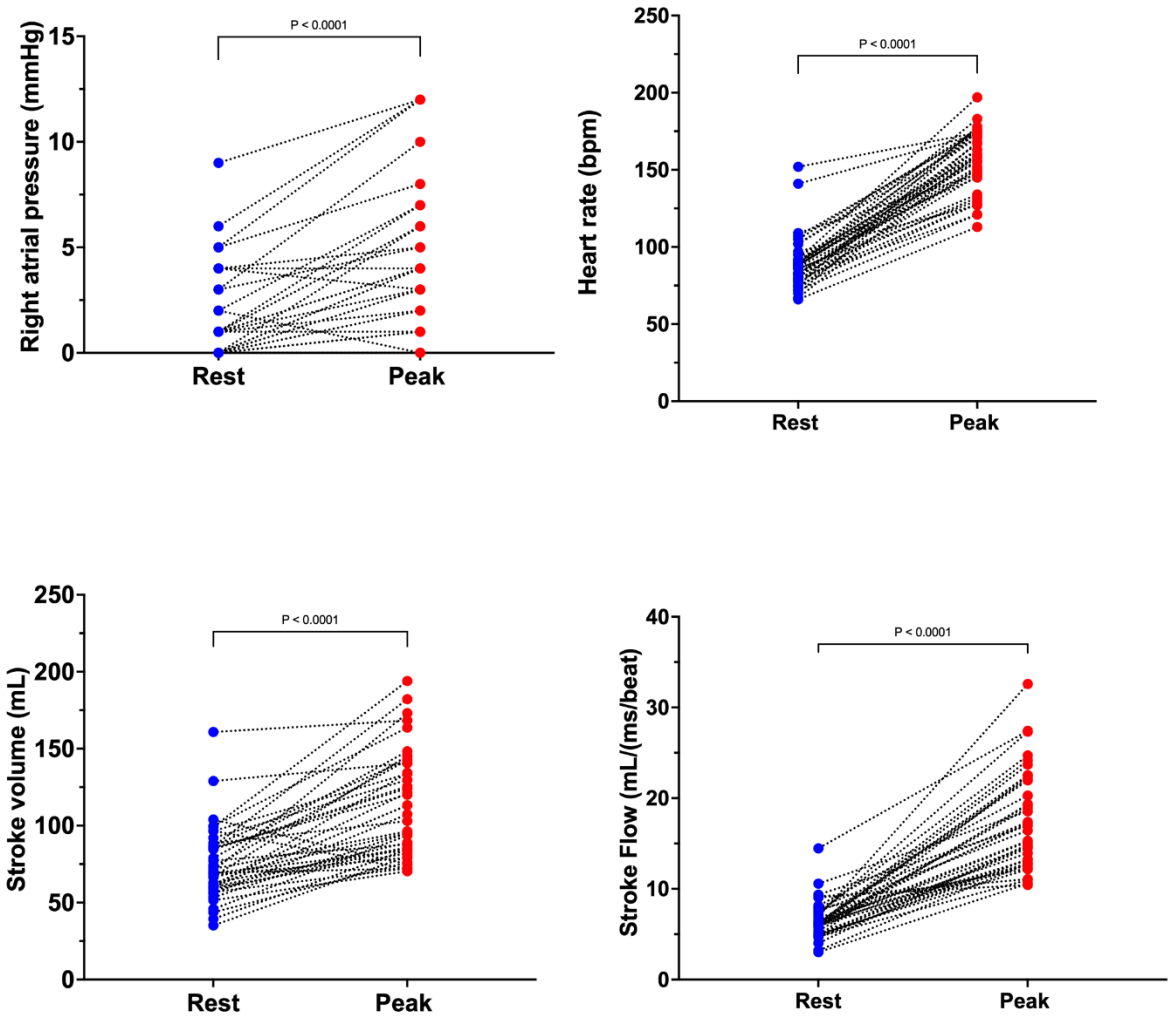
P < 0.0001
Right atrial pressure (mmHg)
15
10
5
0
Rest
Peak
P < 0.0001
Heart rate (bpm)
250
200
150
100
50
0
Rest
Peak
P < 0.0001
Stroke volume (mL)
250
200
150
100
50
0
Rest
Peak
P < 0.0001
Stroke Flow (mL/(ms/beat)
40
30
20
10
0
Rest
Peak

Figure 1