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# Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease



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## ABSTRACT

**OBJECTIVES** The authors used cardiopulmonary exercise testing (CPET) to define unexplained dyspnea in patients with post-acute sequelae of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (PASC). We assessed participants for criteria to diagnose myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

**BACKGROUND** Approximately 20% of patients who recover from coronavirus disease (COVID) remain symptomatic. This syndrome is named PASC. Its etiology is unclear. Dyspnea is a frequent symptom.

**METHODS** The authors performed CPET and symptom assessment for ME/CFS in 41 patients with PASC 8.9 ± 3.3 months after COVID. All patients had normal pulmonary function tests, chest X-ray, and chest computed tomography scans. Peak oxygen consumption (peak  $\dot{V}O_2$ ), slope of minute ventilation to  $\text{CO}_2$  production (VE/ $\dot{V}CO_2$  slope), and end tidal pressure of  $\text{CO}_2$  (Pet $\text{CO}_2$ ) were measured. Ventilatory patterns were reviewed with dysfunctional breathing defined as rapid erratic breathing.

**RESULTS** Eighteen men and 23 women (average age: 45 ± 13 years) were studied. Left ventricular ejection fraction was 59% ± 9%. Peak  $\dot{V}O_2$  averaged 20.3 ± 7 mL/kg/min (77% ± 21% predicted  $\dot{V}O_2$ ). VE/ $\dot{V}CO_2$  slope was 30 ± 7. Pet $\text{CO}_2$  at rest was 33.5 ± 4.5 mm Hg. Twenty-four patients (58.5%) had a peak  $\dot{V}O_2$  <80% predicted. All patients with peak  $\dot{V}O_2$  <80% had a circulatory limitation to exercise. Fifteen of 17 patients with normal peak  $\dot{V}O_2$  had ventilatory abnormalities including peak respiratory rate >55 (n = 3) or dysfunctional breathing (n = 12). For the whole cohort, 88% of patients (n = 36) had ventilatory abnormalities with dysfunctional breathing (n = 26), increased VE/ $\dot{V}CO_2$  (n = 17), and/or hypocapnia Pet $\text{CO}_2$  <35 (n = 25). Nineteen patients (46%) met criteria for ME/CFS.

**CONCLUSIONS** Circulatory impairment, abnormal ventilatory pattern, and ME/CFS are common in patients with PASC. The dysfunctional breathing, resting hypocapnia, and ME/CFS may contribute to symptoms. CPET is a valuable tool to assess these patients. (J Am Coll Cardiol HF 2021;9:927-937) © 2021 by the American College of Cardiology Foundation.

Infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can result in a wide range of illnesses from no symptoms to multisystem failure (1,2). The acute disease process can lead to residual organ damage with long-term sequelae (3). Surveys of patients with coronavirus disease (COVID) who recover from COVID have described persistent symptoms, such as atypical

chest pain, fatigue, palpitations, or dyspnea, months after the initial infection (4,5). In social media these patients are called “long haulers,” whereas in the medical published reports they are referred to as patients with postacute sequelae of SARS-CoV-2 infection (PASC). Many of these patients were never hospitalized. Symptoms associated with PASC can be remitting, relapsing, or disabling and can persist

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**ABBREVIATIONS  
AND ACRONYMS**

<b>AT</b>	= anaerobic threshold
<b>BMI</b>	= body mass index
<b>COVID</b>	= coronavirus disease
<b>CPET</b>	= cardiopulmonary exercise test
<b>CT</b>	= computed tomography
<b>DB</b>	= dysfunctional breathing
<b>FEV1</b>	= forced expiratory volume in 1 sec
<b>HR</b>	= heart rate
<b>LVEF</b>	= left ventricular ejection fraction
<b>ME/CFS</b>	= myalgic encephalomyelitis/chronic fatigue syndrome
<b>peak VO<sub>2</sub></b>	= peak oxygen consumption
<b>PASC</b>	= Post-Acute Sequelae of SARS-CoV-2 infection
<b>P<sub>ET</sub>CO<sub>2</sub></b>	= end tidal pressure of CO <sub>2</sub>
<b>PFT</b>	= pulmonary function test
<b>RA</b>	= right atrial
<b>RER</b>	= respiratory exchange ratio
<b>RR</b>	= respiratory rate
<b>SARS-CoV-2</b>	= severe acute respiratory syndrome-coronavirus-2
<b>SV</b>	= stroke volume
<b>VE</b>	= minute ventilation
<b>VE/VCO<sub>2</sub> slope</b>	= the slope of minute ventilation to CO <sub>2</sub> production

without evidence of residual injury on imaging studies leaving the etiology of postrecovery symptoms undefined (4,5).

Potential mechanisms for this syndrome include pulmonary and/or cardiac dysfunction. Longitudinal changes on chest computed tomography (CT), such as pulmonary fibrosis and vascular changes after recovery, have been described (4). Cardiac dysfunction may be detected with cardiac magnetic resonance after acute COVID infection, but this has not been reported specifically in patients with PASC (6). The major symptoms in PASC include severe fatigue, cognitive difficulty, unrefreshing sleep, and myalgias—all symptoms are consistent with the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This syndrome of unexplained fatigue has been reported after viral infection; in fact, 27% of patients surviving 4 years after the 2005 SARS epidemic fulfilled criteria for ME/CFS (7).

Cardiopulmonary exercise testing (CPET) is frequently used to evaluate unexplained dyspnea and may be valuable in identifying the cause of dyspnea and exercise intolerance in these patients. The addition of hemodynamic monitoring to the respiratory data can identify additional mechanisms, including exercise-induced pulmonary hypertension and preload failure (8,9). Only 3 small single-center reports of CPET studies in post-COVID patients have been described (10-12), and none exclusively focused on PASC. In this study, we performed CPET and

did targeted histories for ME/CFS in 41 patients with PASC.

**METHODS**

**PATIENT POPULATION.** This was a prospective study of patients who had been reverse transcription polymerase chain reaction positive for SARS-CoV-2 and who developed new and persistent shortness of breath for >3 months after recovery. Patients were referred from pulmonologists or cardiologists and had been shown to have normal pulmonary function tests, chest X rays, chest CT scans, and echocardiograms.

**CPET.** Patients reported to the exercise laboratory in the fasting state. Medications were continued. Forced expiratory volume in 1 second (FEV1) was measured using a portable spiograph. Patients were connected to an electrocardiogram, pulse oximeter, and blood

pressure cuff and were seated on a bicycle ergometer (Lode). Using a disposable mouthpiece, they breathed into a metabolic cart (Med Graphics Ultima O<sub>2</sub>). Resting data was collected for 3 minutes and then incremental bicycle exercise was begun at 0 W increasing by 25 W every 3 minutes to exhaustion. Blood pressure and perceived fatigue using the Borg Scale were obtained at each workload and at peak exercise. The reason for terminating exercise was recorded.

Additionally, invasive hemodynamics via a Swan Ganz catheter was performed during exercise on 7 patients who were referred specifically for this testing. Patients performed the CPET as described with measurements of right atrial, pulmonary artery, and pulmonary capillary wedge pressures at rest, at each stage of exercise, and at peak exercise. Blood samples for pulmonary venous saturation and lactate were also obtained at these timepoints.

Before exercise, patients underwent a targeted interview for elements of ME/CFS. The patients were asked to estimate how much during the prior 6 months: 1) had their fatigue reduced their activity at work, in their personal life, and/or in school (Life Spheres criteria); and 2) to quantify symptom burden of sore throat, tender nodes, headache, myalgia, arthralgia, unrefreshing sleep, difficulty concentrating, or worsening of symptoms after mild exertion (Symptom criteria). ME/CFS was considered present if at least 1 life sphere criteria was impacted substantially and at least 4 symptoms were rated moderate or greater (13).

The study was approved by the Investigations Research Committee of the Icahn School of Medicine at Mount Sinai. All patients provided informed consent.

**DATA AND STATISTICAL ANALYSIS.** All continuous variables are presented as mean ± SD. Variables are compared by nonpaired Student's *t*-testing assuming equal variance and reported as significant if 2-tailed *P* < 0.05. Categorical variables are summarized as frequencies and percentages.

Peak oxygen consumption (peak VO<sub>2</sub>) was defined as the highest 30-second average of oxygen consumption and was normalized by the predicted VO<sub>2</sub> (Wasserman equation) to derive a % predicted value. VO<sub>2</sub> pulse equaled the peak VO<sub>2</sub> divided by maximum heart rate (HR). In men the VO<sub>2</sub> pulse ranges from 12-15 mL/beat and in women from 10-12 mL/beat. The ventilatory threshold was identified as the point at which the ventilatory equivalent for O<sub>2</sub> was minimal, followed by a progressive increase. This was considered normal if the ventilatory threshold was >40% of

the predicted  $VO_2$ . Ventilation (VE) carbon dioxide ( $VCO_2$ ) slope was assessed by correlation of VE and  $VCO_2$  throughout the exercise. Normal VE/ $VCO_2$  slope is  $<30$ . Oxygen uptake efficiency slope was determined (14). Maximal voluntary ventilation was estimated as  $35 \times FEV1$ . Breathing reserve was calculated as  $(1 - \text{peak VE}/\text{maximal voluntary ventilation}) \times 100$ . Normal breathing reserve is  $>30\%$ . Hypocapnia was defined as a resting end tidal  $CO_2$  ( $P_{ET}CO_2$ ) below the lower limit of normal ( $<35$  mm Hg) and severe hypocapnia as a  $P_{ET}CO_2 <31$  mm Hg.

Dysfunctional breathing (DB) is rapid erratic breathing. There are no strict criteria and identification is based on pattern recognition (15). We reviewed graphs of VE versus time, and then each parameter- $VCO_2$ , respiratory rate (RR), and tidal volume vs VE (mL/min). Patients who had tachypnea at rest (RR  $>20$ ) with continued rapid respiratory rate with early exercise and a delayed increase in tidal volume were also considered to have DB.

A maximal test was defined as one with a respiratory exchange ratio (RER)  $\geq 1.05$ ; or if the  $VO_2$  was  $<80\%$  predicted then the  $VO_2$  was defined as reduced. Patients with reduced  $VO_2$  and early onset of anaerobic threshold, reduced  $VO_2$  pulse, and elevated VE/ $VCO_2$  slope were classified as having circulatory impairment. Patients with low breathing reserve,  $O_2$  desaturation, or with RR  $>55$  beats/min with exercise were identified as having a ventilatory impairment (16).

For hemodynamic CPET, exercise-induced pulmonary hypertension was defined by a mean pulmonary artery pressure  $\geq 30$  mm Hg and/or a total pulmonary resistance (ie, mean pulmonary artery pressure/cardiac output)  $>3$  WUs. Preload failure was defined as peak right atrial (RA) pressure  $\leq 8$  mm Hg or change in rest to peak exercise RA pressure  $<3$  mm Hg and a peak mean pulmonary artery  $<25$  mm Hg (8,9). Poor systemic oxygen extraction was defined as maximal arteriovenous oxygen difference/hemoglobin of  $\leq 0.8$  (8,9). The relationship between the cardiac output and  $VO_2$  was plotted ( $\Delta Q/\Delta VO_2$ ) with normal approximating 5. High values indicate defects in skeletal muscle blood flow and/or extraction.

**RESULTS**

**BASELINE CHARACTERISTICS.** Forty-one patients (23 women, 18 men) participated with an average age of  $45.2 \pm 12.5$  years (range 23-69 years) and body mass index (BMI) of  $28.3 \pm 6.4$  (range 18.8-41.5). Hemoglobin was  $14.0 \pm 1.3$  g/dL. Fourteen patients had a BMI  $>30$  kg/m<sup>2</sup>. Four patients had diabetes, 9 patients were hypertensive, 2 patients had postural

**TABLE 1 Cardiopulmonary Measurements for All Patients (N = 41)**

	Rest	Peak Exercise	Predicted
Workload (W)		113 ± 40	150 ± 54
HR (beats/m)	83 ± 14	152 ± 26	175 ± 12
MAP (mm Hg)	92 ± 10	104 ± 12	
O <sub>2</sub> sat (%)	98 ± 1	97 ± 2	
VE (L/min)	11.1 ± 2.9	57.2 ± 19.6	
RR (breaths/min)	15.6 ± 5	36 ± 11	
RER	0.9 ± 0.1	1.12 ± 0.1	
VO <sub>2</sub> (mL/kg/min)	4.0 ± 0.8	20.3 ± 7	76.5 ± 21.4
VO <sub>2</sub> AT (mL/kg/min)		11.7 ± 3.2	10.6 ± 2.8
VD/VT	0.26 ± 0.05	0.17 ± 0.04	
PetCO <sub>2</sub> (mm Hg)	33.5 ± 4.5	35.8 ± 5.5	
VO <sub>2</sub> pulse (mL/beat)		10.5 ± 2.9	
VE/ $VCO_2$		30.4 ± 6.8	
OUES		1,867 ± 602	2,450 ± 569
VO <sub>2</sub> work rate (mL/W)		9.7 ± 1.6	10
Borg scale		18 ± 1.8	
Symptom limiting exercise			
Fatigue		15	
Dyspnea		15	
Fatigue and dyspnea		7	
Dizziness		2	
Pleuritic CP		1	
Other		1	

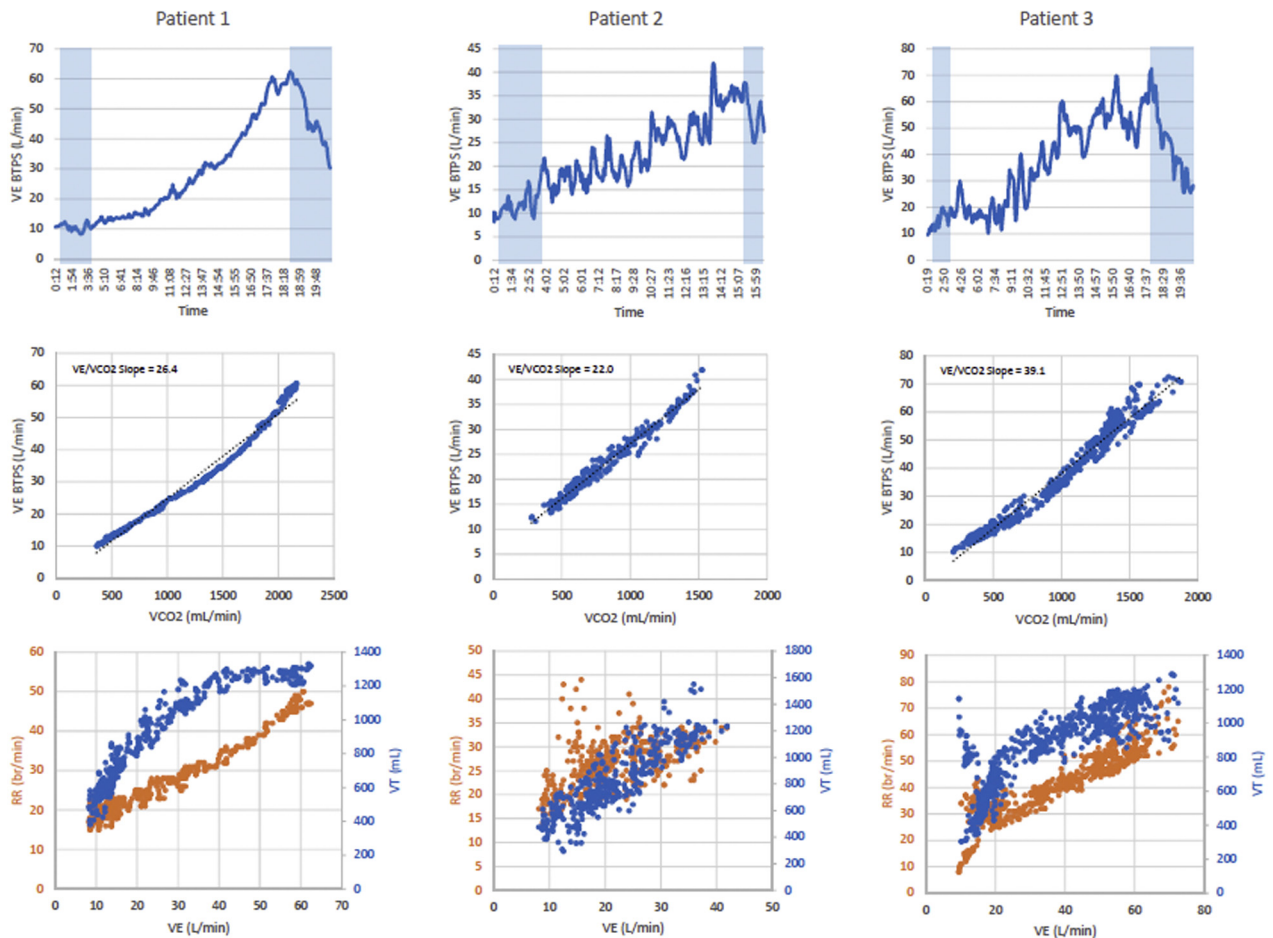
Values are mean ± SD or n.  
 CP = chest pain; HR = heart rate; MAP = mean arterial pressure; OUES = oxygen uptake efficiency slope; PetCO<sub>2</sub> = end tidal CO<sub>2</sub>; RER = respiratory exchange ratio; RR = respiratory rate; VD/VT = dead space to tidal volume ratio; VE = minute ventilation; VE/ $VCO_2$  = ventilatory equivalent for CO<sub>2</sub> production; VO<sub>2</sub>AT = oxygen consumption at anaerobic threshold.

orthostatic tachycardia, 1 patient had a prior atrial fibrillation ablation, and 1 patient had a remote history of colon cancer.

Patients had acute COVID infection an average of  $8.9 \pm 3.3$  months (range 3-15 months) before CPET. Only 9 of the 41 patients were hospitalized. Eight patients were hospitalized with acute COVID (length of stay:  $9.5 \pm 7.2$  days; range 2-25 days; median: 9 days). One was hospitalized after COVID for atypical chest pain. None were intubated. Five received steroids, 2 convalescent plasma, 2 remdesivir, 5 azithromycin, 4 hydroxychloroquine, 2 enoxaparin, and 1 apixaban. Various therapies for the nonhospitalized Patients with COVID were administered with steroid treatment the most common (n = 7) followed by azithromycin (n = 3). Left ventricular ejection fraction (LVEF) on transthoracic echo averaged  $58\% \pm 8.6\%$  and FEV1 averaged  $2.9 \pm 0.9$  L. Thirteen patients were currently receiving beta blocker therapy for treatment of palpitations, hypertension, or atypical chest pain.

**EXERCISE RESULTS.** Table 1 summarizes the exercise parameters for the cohort. Peak  $VO_2$  averaged  $20.3 \pm 7$  mL/kg/min, which was  $77\% \pm 21\%$  of predicted. Every patient reached an anaerobic threshold. Thirty-six patients had RER  $>1.05$  with 3 patients

**FIGURE 1 Patient #1 Shows Normal Ventilatory Pattern in 3 Graphs**



**(Top)** VE increases smoothly over time. **(Middle)** Tight linear correlation of VE and VCO<sub>2</sub>. **(Bottom)** RR (orange, left y axis) and TV (blue, right y axis) is plotted vs minute ventilation (x axis). A slow increase in RR and an early large increase in TV at the start of exercise is observed. Patients #2 and #3 show examples of the dysfunctional breathing. **(Top)** VE vs time in patient #2 and #3 show numerous erratic spikes. **(Middle)** A thicker line correlating VE with VCO<sub>2</sub>. **(Lower)** Dissociation between RR and TV vs VE is observed. Total overlap of RR and TV is seen in patient #2 and an overlap of RR and TV early and late in exercise occurs in patient #3. RR = respiratory rate; VE = minute ventilation; VT = tidal volume.

having a RER of 1.04. Two patients had submaximal tests with a peak RER of 1.0 and 0.98, respectively. Only 4 patients had a breathing reserve <30% with 1 patient also having O<sub>2</sub> desaturation.

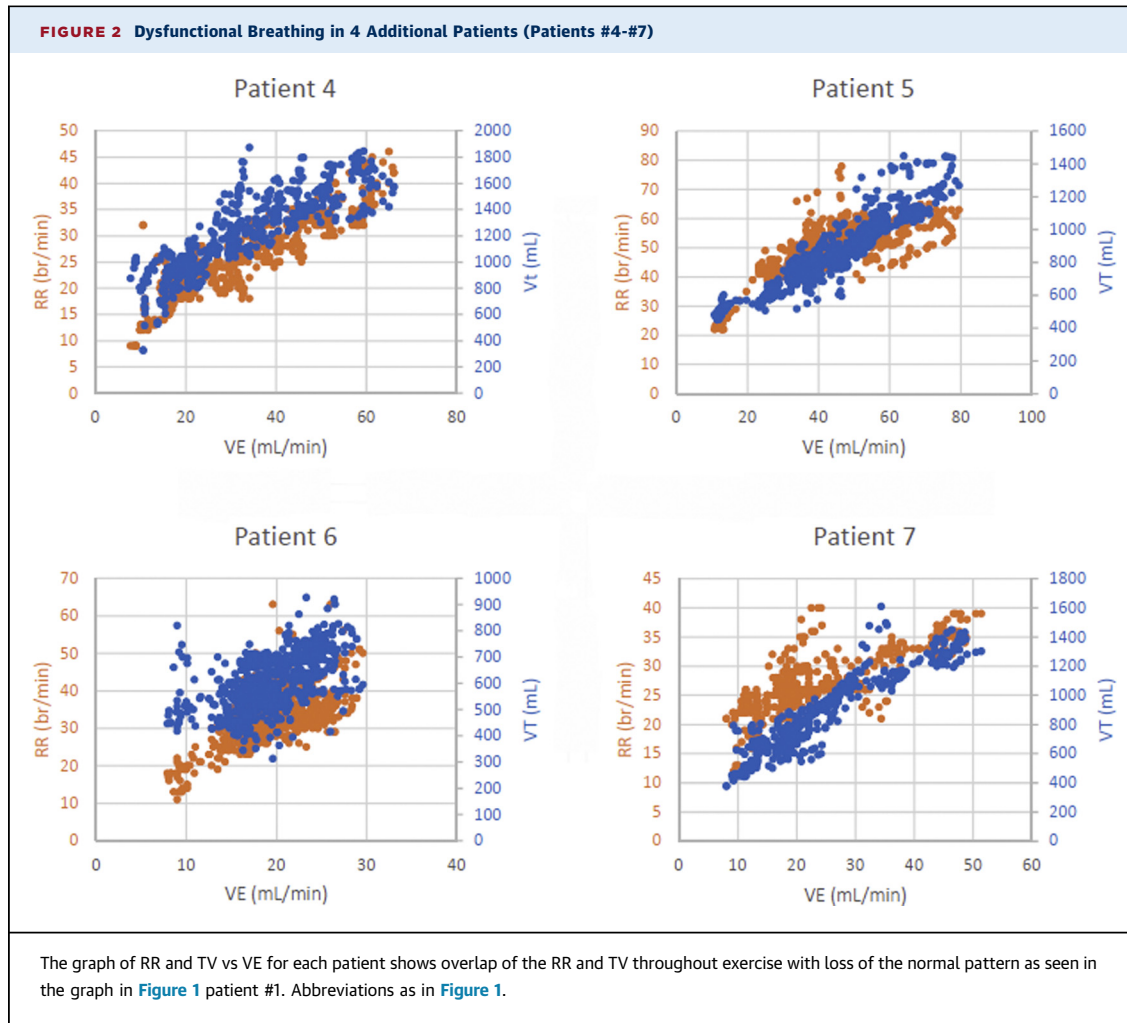
Twenty-four patients had VO<sub>2</sub> <80% of predicted with low oxygen consumption at anaerobic threshold VO<sub>2AT</sub> (n = 12), low VO<sub>2</sub> pulse (n = 22), and/or elevated VE/VCO<sub>2</sub> (n = 23). Fourteen of these patients had DB.

The remaining 17 patients had VO<sub>2</sub> ≥80% predicted, ie, 41% of the patients would be classified as having normal exercise capacity. However, despite having a normal exercise capacity, there were several abnormal findings. Two patients had reduced VO<sub>2</sub> pulse, 3 patients had RR >55 breaths/

min, and 12 had abnormal ventilatory patterns. Importantly, only 2 tests could be classified as completely normal (5%).

**VENTILATORY RESPONSE TO EXERCISE.** The ventilatory pattern during exercise revealed DB in 26 patients (63%). **Figure 1A** shows normal ventilatory pattern in a 47-year-old woman (patient #1) with a steady increase in VE over time, and a tight linear correlation of VE and VCO<sub>2</sub>. A slow increase in respiratory rate with an early large increase in tidal volume at the start of exercise followed by a leveling of tidal volume at moderate to high exertion is observed when graphed against VE. **Figures 1B and 1C** show examples of the DB in a 35-year-old man (patient #2) and a 57-year-old woman (patient #3). Erratic





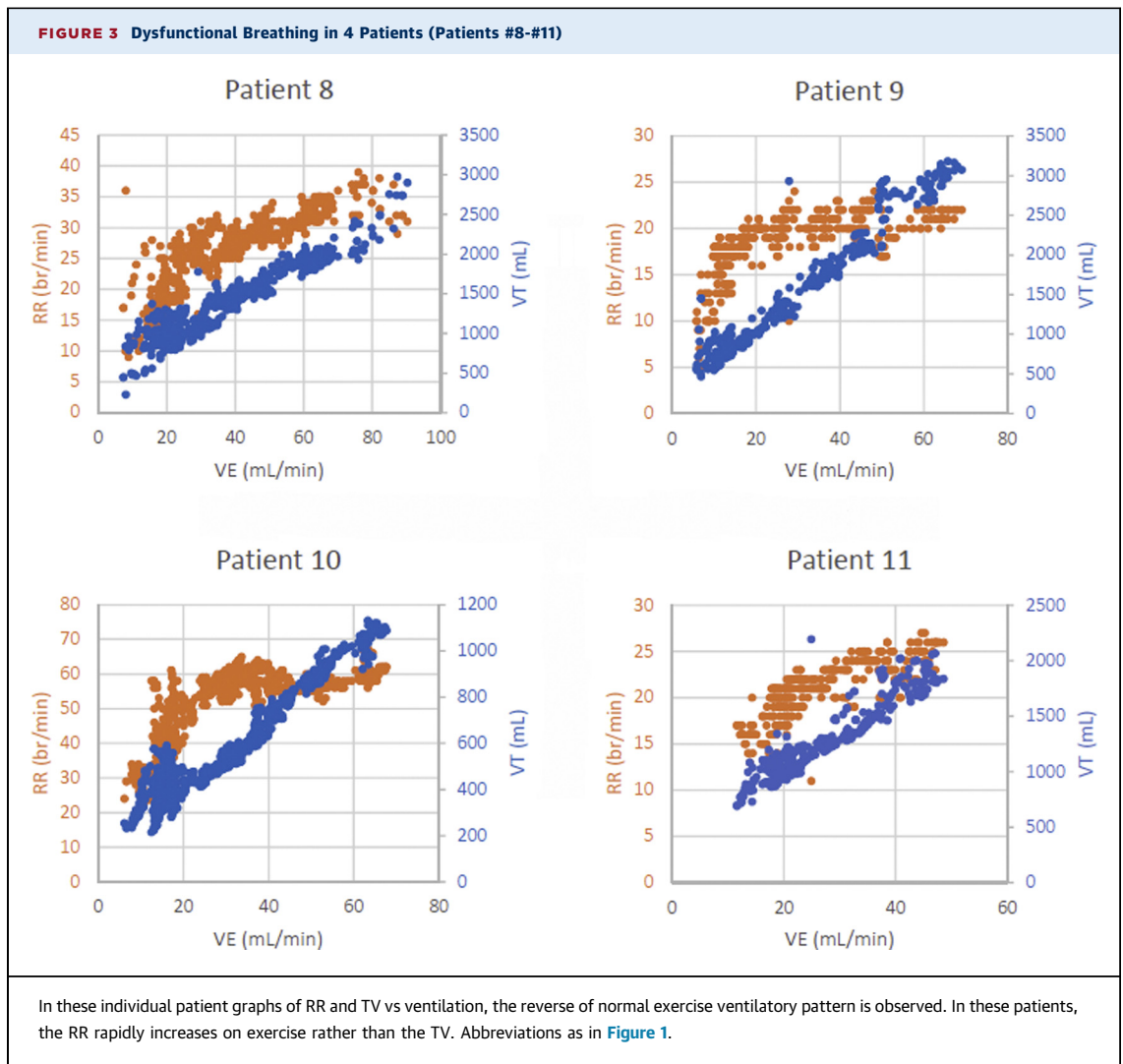
oscillations of ventilation over time, a band-like correlation of VE with  $VCO_2$ , and a dissociation between respiratory rate and tidal volume versus VE is observed in both patient #2 and #3. Figure 2 shows additional examples of the chaotic breathing patterns observed in these post-COVID patients. Some patients had resting tachypnea that continued in early exercise with a delayed rise in tidal volume. This is the reverse of what is seen in normal healthy controls (Figure 3).

Identification of DB is subjective so comparison of patients with and without DB may not be reproducible. In this analysis, those identified as having DB (n = 26) compared with those with a normal breathing pattern (n = 15) revealed no significant differences between these 2 groups for peak  $VO_2$  (DB+:  $19.7 \pm 7.3$ ; DB-:  $22.4 \pm 6.4$  mL/kg/min), resting  $petCO_2$  (DB+:  $33.5 \pm 3.3$ ; DB-:  $33.5 \pm 6.2$  mm Hg), maximum VE (DB+:  $54.6 \pm 20$ ; DB-:  $61.6 \pm 18.2$ ), RR (DB+:  $35.6 \pm 11.2$ ; DB-:  $36.8 \pm 10.8$  L/min), or RER (DB+:  $1.10 \pm 0.06$ ;

DB-:  $1.16 \pm 0.8$ ; all  $P > 0.05$ ). Measurements of  $PetCO_2$  were lower than those observed in normal subjects at rest and with exercise. Normal  $PetCO_2$  at rest is 35-45 mm Hg with an increase of about 5-8 mm Hg with exertion. Also, 61% of patients (n = 25) had resting  $PetCO_2$  lower than 35 mm Hg.  $PetCO_2$  at rest, anaerobic threshold (AT), and peak exercise were  $33.5 \pm 4.5$ ,  $38.9 \pm 4.8$ , and  $35.8 \pm 5.5$  mm Hg, respectively ( $P < 0.0001$ ). Most patients had an appropriate increase in  $PetCO_2$  at with decrease at peak exercise. However, 3 patients showed continued low  $PetCO_2$  throughout exercise.

Analysis was also performed excluding morbidly obese patients (BMI  $>35$  kg/m<sup>2</sup>; n = 8). For the patients with BMI  $<35$  kg/m<sup>2</sup>, 64% had peak  $VO_2 <80\%$  predicted, 52% elevated VE/ $VCO_2$ , 67%, reduced  $PetCO_2$ , and 60% DB.

**HEMODYNAMIC CPET RESULTS.** Seven patients underwent invasive CPET, including 3 men and 4 women with a mean age of  $57 \pm 4.4$  years (Table 2).



Hemoglobin averaged  $13.6 \pm 1.6$  g/dL. Although 4 of the 7 patients would be classified as having normal  $\dot{V}O_2$  (peak  $\dot{V}O_2 > 80\%$  predicted), 5 of the 7 patients (#1-#4 and #6) had preload failure. [Figure 4](#) shows the increase in stroke volume during exercise. Average increase in stroke volume in patients with preload failure was  $18 \pm 11$  mL/beat. These 5 patients also had borderline systemic oxygen extraction ratios ranging from 0.83-0.88. All 5 patients with preload failure had symptoms consistent with ME/CFS, but only 3 met criteria (1 was excluded for BMI  $> 30$  kg/m<sup>2</sup> and one for a LVEF  $< 50\%$ ). Patients #5 and #7 had hemodynamics consistent with exercise-induced pulmonary hypertension and did not meet criteria for ME/CFS.

**ME/CFS CLASSIFICATION.** Thirty-two patients met the 1994 criteria for ME/CFS (11). However, ME/CFS is a diagnosis of exclusion and we excluded 4 patients with cardiac disease (3 with mid-range LVEF; 1 with

chronic pericardial effusion) and 9 patients with a BMI  $> 30$ , leaving 19 of the 41 patients (46%) with the diagnosis of ME/CFS. Chronic hyperventilation has been associated with ME/CFS (20), and we find that same result here (7 of 19 had  $\text{PetCO}_2 \leq 31$  mm Hg). This result was not different from patients who did not have ME/CFS (6 of 22 had  $\text{PetCO}_2 \leq 31$  mm Hg). Eight (42%) patients who met the criteria for ME/CFS also had DB; this was similar to rates of DB in those who did not have ME/CFS (12 of 21; 57%).

## DISCUSSION

In this observational report of CPET in patients with PASC, there are several notable findings. First, almost all patients (88%) exhibited variability in ventilation consistent with DB, resting hypocapnia, and/or an excessive ventilatory response to exercise (elevated  $\text{VE}/\text{VCO}_2$  slope). Second, the majority of the patients

**TABLE 2 Hemodynamic Measurements for Patients With Invasive CPET**

Patient #	Gender	Age	VO <sub>2</sub>	HR	MAP	RER	RA	mPA	PCW	CO	AVO <sub>2</sub>	SVI	
1	M	50	3.8	81	110.0	0.87	6	12	4	9.5	4.1	52	
2	F	55	3.3	70	88.7	0.76	0	4	1	4.66	5.0	42	
3	M	61	4.3	63	92.0	0.79	2	8	6	4.68	6.8	37	
4	F	57	4.0	71	96.7	0.82	0	3	1	3.98	6.3	32	
5	M	60	5.2	73	95.3	0.80	0	9	1	6.40	6.8	44	
6	M	56	3.1	71	94.0	0.84	0	8	1	6.73	3.7	47	
7	F	60	3.3	83	102.6	0.82	4	12	5	4.30	5.4	31.3	
			57.00 ± 8.29	3.86 ± 4.60	73.14 ± 10.37	97.04 ± 12.04	0.81 ± 3.94	1.71 ± 6.51	8.00 ± 7.60	2.71 ± 6.20	5.75 ± 6.13	5.44 ± 5.10	40.76 ± 11.44
Peak EX													
	Peak VO <sub>2</sub>	HR	MAP	RER	RA	mPA	PCW	CO	AVO <sub>2</sub>	SVI	% PredVO <sub>2</sub>		
1	ME/CFS	22.2	160	123.0	1.07	8	24	17	19.00	12.0	53	86	
2		16.4	119	86.7	1.10	0	18	15	9.78	9.5	52	70	
3	ME/CFS	28.7	162	104.7	1.14	8	23	10	16.60	12.9	52	101	
4	ME/CFS	24.8	178	96.7	1.10	5	13	10	14.50	10.6	47	112	
5	ME/CFS	31.2	157	104.0	1.15	6	36	17	17.90	14.9	57	111	
6	ME/CFS	22.7	147	113.0	1.17	0	22	12	16.60	11.3	57	76	
7		10.0	130	106.7	1.06	12	31	13	9.16	7.7	42.7	53	
		22.29 ± 12.42	150.43 ± 25.39	104.97 ± 16.72	1.11 ± 5.24	5.57 ± 9.59	23.86 ± 12.89	13.43 ± 8.19	14.79 ± 9.09	11.27 ± 7.53	51.53 ± 10.38	87.00 ± 27.43	

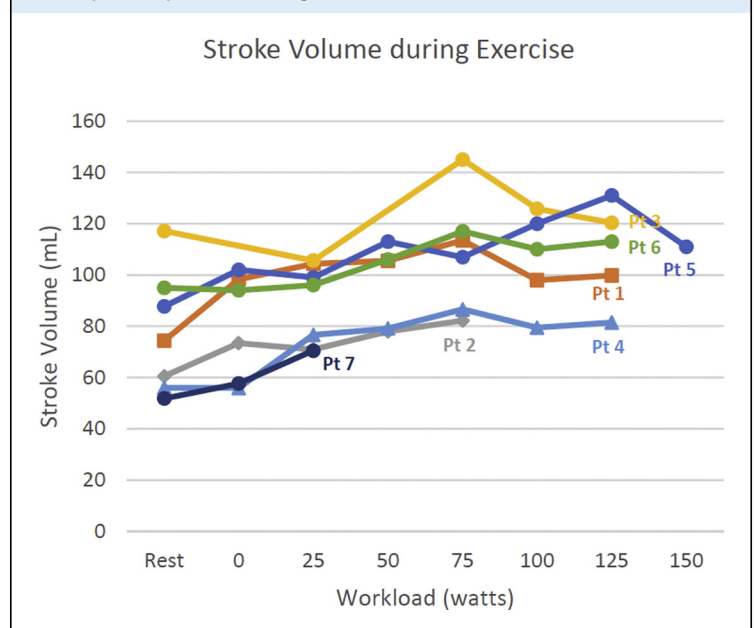
Values are n, %, or mean ± SD.  
 CO = cardiac output; EX = exercise; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; mPA = mean pulmonary artery pressure; PCW = pulmonary capillary wedge; RA = right atrial; SVI = stroke volume index.

(58%) had evidence of circulatory impairment to peak exercise performance. Finally, a large percentage (46%) met criteria for ME/CFS.

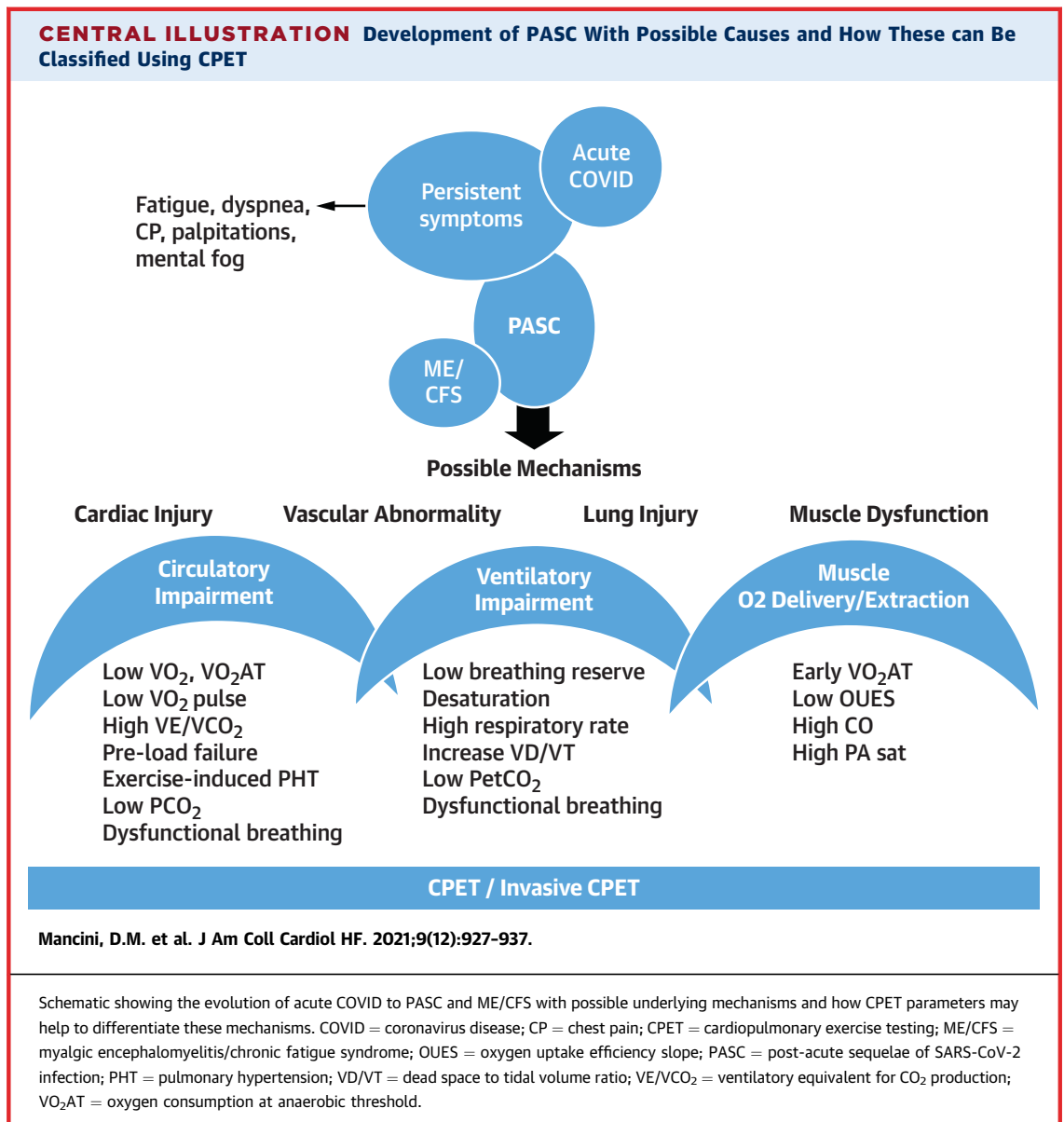
Recovery from the acute COVID-19 infection can be associated with residual organ damage and long-term sequelae, which has been described as PASC (Central Illustration). Many of these patients report dyspnea. CPET has been used to determine the etiology of unexplained dyspnea. The Central Illustration shows the progression from acute COVID infection to PASC and how CPET can assist in classifying the etiology.

**CPET IN PASC.** There are few reports using CPET in patients with PASC. Montiejuanaite et al (10) reported on 8 patients with symptoms 3 months after COVID infection. Seven patients were women and none was hospitalized. Similar to our patient cohort, pulmonary function tests (PFTs), chest CT, and echocardiograms were normal. Six patients had a peak VO<sub>2</sub> <80% predicted and all had elevated VE/VCO<sub>2</sub>. These authors speculated that exercise hyperventilation contributed to the persistent symptoms. We

**FIGURE 4 Stroke Volume During Rest and Exercise in the 7 Patients With Invasive Cardiopulmonary Exercise Testing**







also found 3 patients with exercise hyperventilation, a large percentage with resting hypocapnia and DB, which leads us to also suggest that hyperventilation contributes to PASC.

Clavario et al (11) reported CPET results in 110 patients with “nonsevere” COVID 3 months after the infection. Approximately 70% of these patients had persistent symptoms. PFTs were normal. Also, 36% had a peak  $VO_2$  <85% predicted. These investigators attributed the reduction in  $VO_2$  to muscle impairment because a weak correlation was observed between lower maximal muscle strength and % predicted  $VO_2$ . Generally, muscle mass predicts a subject’s ability to perform isometric rather than isotonic exercise.

Similar to this report, 58% of our patients had reduced peak  $VO_2$ .

**CIRCULATORY LIMITATION TO EXERCISE.** All of our PASC cohort with reduced  $VO_2$  exhibited a circulatory impairment to exercise. Circulatory impairment includes both intrinsic cardiac disease and/or abnormalities in pulmonary or peripheral perfusion. Cardiac magnetic resonance studies soon after COVID have demonstrated persistent myocardial inflammation or scar suggesting altered cardiac function (6). Correlation of imaging studies to CPET results is lacking. Circulatory impairment also includes reduced lung perfusion, which may be particularly important in producing dyspnea. COVID

has been associated with significant clot formation including pulmonary emboli (3). It is possible that some patients may have thromboembolic pulmonary disease. Two patients who underwent invasive CPET had evidence of exercise-induced pulmonary hypertension.

The other patients who underwent invasive CPET had hemodynamic measurements consistent with preload failure with a blunted increase right atrial pressure during exercise (8,9). Preload failure, described in patients with unexplained dyspnea and ME/CFS (9), may be caused by reduction in plasma volume causing hypovolemia. In healthy individuals during exercise, the Frank-Starling mechanism increases stroke volume by approximately 40%. Although there is debate as to how much stroke volume (SV) contributes to exercise cardiac output, most investigators describe an increased SV early in exercise, which plateaus or even decreases at peak exercise (17). This increase in SV is primarily achieved by increasing venous return. Lack of increase in RA pressure suggests blunted venous return. A decrease in cardiac output with lung hypoperfusion can contribute to VQ mismatching with a subsequent excessive ventilatory response to exercise as well as abnormal ventilatory patterns (18). Because of this, PetCO<sub>2</sub> measured in PASC may not accurately reflect arterial partial pressure of carbon dioxide because increased ventilation-perfusion mismatching will lower PetCO<sub>2</sub>.

Autonomic dysfunction has also been postulated as contributing to PASC. Sinus arrhythmia is heart rate variability that is linked to the respiratory cycle. During inspiration, thoracic pressure is decreased, the chest cavity expands, air flows into the lungs, arterial blood pressure is lowered, which activates the arterial baroreceptors, vagal tone is suppressed, and heart rate increases. During expiration the reverse occurs. DB can interrupt this cardiopulmonary interaction and result in increase in dead space ventilation and intrapulmonary blood shunting (19).

**VENTILATORY RESPONSE IN PASC.** In our study, a primary ventilatory limitation to exercise was not seen. This is not surprising because we selected patients who had normal PFTs, chest X rays, and CT scans. However, the use of CPET in these patients revealed several resting and peak exercise ventilatory variables that were abnormal.

Many patients with PASC had a rapid, irregular breathing pattern consistent with DB. DB is most often reported in asthmatic patients (20). Prolonged hypoxemia, metabolic abnormalities, and/or anxiety

can trigger DB. It is associated with chronic hypoventilation syndromes and is characterized by rapid shallow breaths with or without hypocapnia (20,21). More than one-half of our patients had PetCO<sub>2</sub> <35 mm Hg. Low PetCO<sub>2</sub> correlates with lower cardiac output both at rest and with exercise. Whether patients with PASC have an abnormal PaCO<sub>2</sub> set point or enhanced CO<sub>2</sub> sensitivity cannot be determined from these data. Arterial partial pressure of carbon dioxide measurements are needed.

DB and persistent hypocapnia can be associated with many of the symptoms experienced by patients with PASC, such as dyspnea, fatigue, chest pain, and palpitations. The identification of DB and resting hypocapnia in this cohort is an important observation because it may represent a target for treatment. Breathing retraining can be effective in relieving symptoms (22). Could DB cause the sensation of dyspnea? Killian and Jones (23) decades ago popularized the theory that the sensation of dyspnea occurs when the activity and/or the work of the respiratory muscles increase or if these muscles are weak. In many of these patients with PASC, tachypnea at low levels of exertion suggests increased respiratory muscle activity, which may lead to the sensation of dyspnea.

**ME/CFS IN PASC.** To the best of our knowledge, this is the first report to indicate a high rate of patients with PASC fulfilling criteria for ME/CFS (46%), which is consistent with what was found after the SARS COVID-19 outbreak (7). One difference between patients with PASC and those with ME/CFS independent of COVID is the frequent report of chest pain, cough, and palpitations. Further research comparing the 2 cohorts will be needed to determine if they are the same or different. The fact that all cases of COVID ME/CFS followed infection and are of short duration will reduce much of the heterogeneity seen in the non-COVID ME/CFS population, which can be associated with a variety of disease processes.

Diagnosis of ME/CFS is subjective without any objective biomarkers or imaging studies, although many patients have low resting PetCO<sub>2</sub> (24). The frequency of hypocapnia was similar in those patients with PASC with and without ME/CFS. CPET has been performed in patients with ME/CFS and peak VO<sub>2</sub> is either mildly reduced or normal (25). DB has not been described, although elevated ventilatory efficiency has been reported.

**STUDY LIMITATIONS.** It is a small single-center observational study using normal values as the

comparator. Consecutive patients presenting to our hospital for post-COVID care were not referred and thus there may be selection bias. We did not measure arterial blood gases during exercise so we cannot determine if the PaCO<sub>2</sub> set point for ventilation was altered because using PetCO<sub>2</sub> to estimate PaCO<sub>2</sub> may not be accurate. With noninvasive CPET, the classification into pulmonary, cardiac, or muscle function as the primary limitation to exercise can be problematic. Further study is needed with patients undergoing CPETs with hemodynamic and arterial gas measurements. Correlation of CPET findings to lung and cardiac imaging should also be performed.

### CONCLUSIONS

Most patients with PASC have circulatory impairment to exercise with DB, suggesting reduced perfusion, especially pulmonary hypoperfusion. Many patients with PASC can also be classified as having ME/CFS. DB, and chronic hyperventilation, may underlie the symptoms of PASC. Use of CPET may be effective in objectively identifying abnormalities associated with PASC that could be targeted for treatment.

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### PERSPECTIVES

#### COMPETENCY IN MEDICAL KNOWLEDGE:

Approximately 20% of patients who recover from an acute COVID infection remain symptomatic with dyspnea and fatigue despite normal cardiac and pulmonary function. CPET can be used to define the cause of unexplained dyspnea.

#### COMPETENCY IN PATIENT CARE:

There is no diagnostic test to define this disorder or current therapies to relieve symptoms.

**TRANSLATIONAL OUTLOOK 1:** Although this study included a small cohort of patients, CPET was able to identify significant abnormalities that can be used to diagnosis the syndrome and potentially guide treatment.

**TRANSLATIONAL OUTLOOK 2:** Almost 50% of these patients met criteria for ME/CFS.

despite hemodynamic and pulmonary abnormalities. *Circulation*. 1988;77:552-559.

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