Circulation: Heart Failure

RESEARCH LETTER

Physiologic Insights Into Long COVID Breathlessness

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Breathlessness is among the most prevalent features of long COVID.[1] While post-COVID lung pathology, such as pulmonary fibrosis, has been reported in some patients, this is not universal. In the absence of direct pulmonary pathology, there has been speculation on the potential contribution of other cardiopulmonary mechanisms, including pulmonary embolism/chronic thromboembolic pulmonary vascular disease, myocardial fibrosis, and microvascular dysfunction. To date, the potential contribution of these latter mechanisms to exertional breathlessness remains controversial and several have not yet been examined in detail using relevant methodologies. In the present study, we aimed to characterize the hemodynamic and metabolic profile patients with long COVID breathlessness at rest and during exertion.

The data that support the findings of this study are available from the corresponding author upon reasonable request. We performed simultaneous echocardiography, right heart catheterization, invasive arterial blood pressure monitoring and blood gas monitoring at rest and during symptom limited exertion in 12 consecutive patients with post-COVID breathlessness, in which a pulmonary cause had been excluded by their managing physician; data were compared with that from 12 age-matched healthy volunteers from prior studies. The study was approved by the Alfred Hospital Research and Ethics Committee, and all participants provided written informed consent. Data are reported as mean±SD. Between group comparisons were performed using an unpaired *t* test.

Patients with COVID were aged 50±6 versus 52±2 years in controls (*P*=ns) and tended to be heavier, albeit not significantly (body mass index: 31±3 versus 26±1 kg/m^2; *P*=ns). Of the patients with COVID, 4 required hospital admission and 2 required intensive care admission. All patients with COVID had significant functional limitation (7 New York Heart Association III and 5 New York Heart Association II). The left ventricular ejection fraction at rest was lower in patients with COVID (66±5% versus 70±4%; *P*=0.03) and the left ventricular end diastolic index was smaller (23±2 versus 25±3 mm/m^2; *P*=0.03). As shown in the Table, patients with COVID exhibited normal resting hemodynamics. Patients with COVID had a significantly lower peak work capacity compared with controls, and the peak exercise cardiac index was lower in patients with COVID. The arterial O_2 saturation, arterial P_{CO_2} and mixed venous O_2 saturation were similar in COVID and control patients at rest and during exercise. Notably the resting arterial lactate concentration was higher in patients with COVID at rest but given the lower peak workload level rose to a lesser extent during exercise.

Our data demonstrate that patients with persistent symptoms of dyspnea post-COVID without significant lung pathology, have normal pulmonary arterial pressures, filling pressures and pulmonary vascular resistance both at rest and during exertion, and show no evidence of oxygen desaturation or accumulation of carbon dioxide. Although we did not conduct a radiological assessment for chronic pulmonary thromboembolic disease in all patients, these data would tend to preclude such a diagnosis. In this cohort of long COVID patients, we, therefore, cannot ascribe a cardiopulmonary cause to the sensation of breathlessness. Although our study is of a relatively small size, we conducted a detailed invasive hemodynamic and echocardiographic assessment at rest and during exercise.

An extensive body of literature has already accumulated to suggest involvement of the cardiovascular

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Table. Rest and Exercise Hemodynamic and Metabolic Features

Parameter	Control	COVID	*P* value
Rest			
MAP, mm Hg	93±3	98±3	0.13
Heart rate, bpm	62±4	70±4	0.19
RAP, mm Hg	5±1	4±1	0.33
PA_m, mm Hg	14±1	15±1	0.18
PCWP, mm Hg	8±1	8±1	0.97
CI, L/min per m^2	2.9±0.2	2.7±0.2	0.44
PVR, mm Hg/L per minute	1.0±0.1	1.3±0.1	0.12
Hb, g/dL	147±3	143±2	0.25
Arterial O_2 saturation, %	98±1	97±1	0.27
PA O_2 saturation, %	75±1	75±2	0.76
Arterial CO_2, mm Hg	36±1	36±2	0.94
Arterial lactate, mmol/L	0.78±0.08	1.30±0.14	0.007
Exercise			
Peak workload, Watts	122±13	58±8	<0.001
MAP, mm Hg	120±4	109±2	0.04
Heart rate, bpm	123±4	105±6	0.03
PA_m, mm Hg	29±2	24±2	0.07
PCWP, mm Hg	16±2	13±2	0.40
CI, L/min per m^2	7.2±0.3	5.5±0.5	0.007
PVR, mm Hg/L per minute	1.0±0.1	1.0±0.1	0.81
Arterial O_2 saturation, %	97±1	98±1	0.81
PA O_2 saturation, %	47±2	53±2	0.06
Arterial CO_2, mm Hg	37±1	34±3	0.30
Arterial lactate, mmol/L	5.6±0.8	2.5±0.3	0.004

Data are mean±SEM. *P* values: unpaired Student *t* test. CI indicates cardiac index; Hb, hemoglobin; MAP, mean arterial pressure; PA, pulmonary artery; PA_m, PA mean pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; and RAP, right atrial pressure.

system in COVID illness. Early reports identified the frequent occurrence of increased levels of cardiac injury biomarkers particularly in patients with severe COVID illness,[2] potentially due to acute plaque rupture, microvascular damage, or myocarditis. The demonstration of COVID mediated acute myocardial injury has also been proposed to contribute to myocardial fibrosis observed in some patients following COVID illness.[3] Patients with acute respiratory distress syndromes not due to COVID have also been shown to have comparable increases in troponin suggesting elevation of cardiac biomarkers is not specific to COVID per se. In this study, we do not have data about cardiac function or troponin profiles during the acute COVID illness.

Critical illness is frequently followed by a protracted recovery phase, due to acquired respiratory and peripheral muscle weakness, impaired cognition and posttraumatic stress. Consistent with observations in chronic fatigue patients,[4] we found a modestly elevated resting blood lactate level in long COVID patients, although exercise was not associated with excess lactate accumulation or limiting oxygen extraction. Alterations in autonomic function may also occur postviral and postcritical illness, manifest by an impairment in volume recruitment during physical activity. Indeed, aspects of our study are consistent with this physiology, as also observed recently.[5] Cardiopulmonary exercise test evaluation was not performed in the current study; recent data have demonstrated markedly reduced peak VO2 in long COVID patients.[5] Taken together, our data are more consistent with long COVID dyspnea being the result of a generalized postcritical illness process rather than a primary cardiovascular cause. Although the current study suggests that post-COVID breathlessness is likely not due to central cardiovascular or pulmonary vascular complications, there does remain an important role for comprehensive cardiopulmonary evaluation in patients with unexplained breathlessness, including long COVID. Such an assessment should include cardiopulmonary exercise testing and invasive exercise hemodynamic studies.

ARTICLE INFORMATION

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Disclosures

None.

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