Short- and long-term noninvasive cardiopulmonary exercise assessment in previously hospitalised COVID-19 patients

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In previously hospitalised COVID-19 patients, noninvasive cardiopulmonary exercise testing demonstrated interval improvement in peak exercise aerobic capacity between 3 and 12 months following hospitalisation https://bit.ly/3BVWwrK

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has had a staggering impact on the global healthcare system [1]. It was estimated that by November 2021, over 3 billion individuals or 44% of the world's population had been infected with SARS-CoV-2 at least once [2]. A substantial number of survivors of COVID-19 exhibit chronic signs and symptoms of multi-systemic illness [3, 4]. This so-called post-acute sequelae of SARS-CoV-2 infection (PASC) syndrome describes a phenomenon that ranges from persistent neurocognitive deficits to cardiorespiratory symptoms beyond 4 weeks from acute disease onset [1]. In general, cardiorespiratory symptoms after COVID-19 can be categorised into two clinical entities. The first is directly related to organ injury or iatrogenic consequences during the acute phase, and the second clinical entity includes an objective decrease in exercise capacity on cardiopulmonary exercise testing (CPET) with normal pulmonary function testing (PFT), resting echocardiogram and computed tomography (CT) scan of the chest [5–8]. Accordingly, CPET is commonly implemented in patients with PASC syndrome to better understand their persistent exertional intolerance [6, 7, 9–11].

In the current issue of the *European Respiratory Journal*, Ingul *et al.* [12] reported on noninvasive treadmill CPET findings in previously hospitalised COVID-19 patients at 3 and 12 months following discharge in a prospective, longitudinal, multicentre study. The study population was accrued from six different institutions across Norway and consisted of a heterogenous population of post-COVID-19 patients, including 20% who required intensive care unit admission. In total, 190 patients underwent CPET at 3 months and 177 patients at 12 months. The authors demonstrated that at 3 and 12 months, 64 patients (34%) and 40 patients (23%), respectively, demonstrated depressed peak exercise aerobic capacity (*i.e.* peak oxygen uptake (V'_{O_2}) ⩽80% predicted). The authors concluded that amongst those with depressed peak V'_{O_2} at months 3 and 12, nearly half (48%) were "deconditioned". The remainder of patients with reduced peak V'_{O_2} at 3 months were reported to have a circulatory limitation (28%), ventilatory limitation (17%), and dysfunctional breathing (7%), while at 12 months, circulatory (33%) and ventilatory limitations (19%) were the other reported reasons for depressed peak V'_{O_2}. While there was interval improvement in peak V'_{O_2}, aerobic exercise capacity at the anaerobic threshold (AT), and peak oxygen pulse at 12 months, previously hospitalised COVID-19 patients report persistent dyspnoea (on Borg CR10 scale) and exhibit depressed peak V'_{O_2} when compared to age and sex-matched controls [13]. At 3 and 12 months, approximately 14% and 22% of patients, respectively, underwent rehabilitation. Whether the rehabilitation programme objectively improved the peak V'_{O_2} in this subgroup of patients was not reported.

The authors are to be commended on the execution of this multicentre longitudinal study, which undoubtedly provides some reassurance to post-COVID-19 patients and treating physicians alike, by demonstrating the interval improvement in peak exercise aerobic capacity 1 year following hospitalisation.

However, like prior noninvasive CPET studies, the current study reported by Ingul *et al.* [12] does not offer a comprehensive pathophysiological rationale for the persistent exertional intolerance experienced by these patients [14]. Specifically, without invasive haemodynamic data and blood gas analysis, the authors were not able to examine if their previously hospitalised post-COVID-19 patients experienced a primary peripheral limit to exercise characterised by impaired systemic oxygen extraction (E_{O_2}) [6, 8].

According to the Fick principle, in the absence of a pulmonary mechanical limitation, reduced peak V'_{O_2} is the result of a blunted cardiac output (CO) response, impaired systemic E_{O_2}, or both. A study involving invasive CPET (iCPET) in 10 patients with persistent exertional limitation 11±1 months after mild COVID-19 found that peak V'_{O_2} was limited primarily by impaired systemic E_{O_2} when compared to age- and sex-matched controls [6]. Importantly, this disparity was evident despite a peak heart rate response and oxygen delivery (D_{O_2}) that was similar between both post-COVID-19 and control subjects. All 10 patients did not require hospitalisation, and none had abnormalities evident on chest CT imaging, PFT or resting echocardiogram, and all had normal haemoglobin levels. In the current study by Ingul *et al.* [12], deconditioning was defined as a peak V'_{O_2} ⩽80% predicted without evidence of ventilatory limitation (*i.e.* normal breathing reserve) or circulatory abnormality (*i.e.* unremarkable electrocardiogram with normal ventilatory efficiency, normal oxygen pulse, and normal or low V'_{O_2} at AT). With the myriad of noninvasive CPET parameters required to fulfil its definition, deconditioning remains a diagnosis of exclusion. Although patients who are deconditioned can exhibit impaired E_{O_2} with exercise [15], in the aforementioned iCPET cohort, preservation of their capacity to increase heart rate and CO adequately at peak exercise makes deconditioning a less likely singular explanation for their exercise limitation. In fact, several patients included in the study had already completed supervised exercise rehabilitation programmes by the time of their iCPET.

It is worth noting the close overlap between the clinical presentation, iCPET findings and peripheral neurovascular dysregulation observed in PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [7, 16, 17]. Impaired systemic E_{O_2} and small fibre neuropathy have been both observed in PASC and ME/CFS [17–20]. Furthermore, the causal hypothesis of ME/CFS has also been linked to preceding infection, including respiratory viruses [21, 22]. This close clinical and neuro-pathophysiological association between PASC and ME/CFS warrants further exploration. In the study reported by Ingul *et al.* [12], the average peak V'_{O_2} at 3 and 12 months in hospitalised post-COVID-19 patients were preserved (*i.e.* peak V'_{O_2} ⩾80% predicted) and despite the interval improvement in peak V'_{O_2} at 12 months, the values of perceived dyspnoea on the Borg CR10 scale were similar at 3 and 12 months, and 85 patients continued to report dyspnoea at 12 months. In ME/CFS patients with persistent exertional intolerance, there can be a disconnect between a "normal" peak V'_{O_2} (*i.e.* peak V'_{O_2} ⩾80% predicted) and a supra-normal CO (*e.g.* on average peak CO is approximately 100% predicted) [17]. In this pathophysiological scenario, the reduced peak V'_{O_2} relative to the supra-normal CO with preserved D_{O_2} is a function of an impaired systemic E_{O_2} [17]. It is therefore plausible that in the study by Ingul *et al.* [12], the persistent dyspnoea experienced at 12 months despite interval improvement in peak V'_{O_2} maybe the consequence of persistently impaired systemic E_{O_2}. One possible explanation for the impaired systemic E_{O_2} is a mismatch between systemic micro-circulatory perfusion and mitochondrial oxidative metabolism. A left-to-right systemic arterio-venous shunt process has been observed in small fibre neuropathy [17], while a recent study has suggested a potential role of mitochondrial dysfunction in PASC patients [23].

The COVID-19 pandemic has led to a dramatic loss of human life and presents an unprecedented challenge to our global healthcare systems. The severity of acute SARS-CoV-2 infection and its associated mortality and hospitalisation rates have been mitigated with the advent of vaccines [24] and various acute pharmacotherapeutic options [25–28]. However, for patients with PASC, their ongoing symptomatology persists and may even have implications beyond exercise intolerance [29]. While the interval improvement in aerobic exercise capacity reported in the study by Ingul *et al.* [12] offers some reassurance, future studies focused on accurate cardiopulmonary–systemic vascular haemodynamic assessment coupled with advanced "omics" molecular phenotyping are warranted to help better understand the patho-mechanistic process that begets PASC and thus develop therapeutic options for our patients.

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