EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Editorial

Short and Long Term Non-Invasive Cardiopulmonary Exercise Assessment in previously Hospitalized COVID-19 Patients

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Please cite this article as: Singh I, Joseph P. Short and Long Term Non-Invasive Cardiopulmonary Exercise Assessment in previously Hospitalized COVID-19 Patients. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.01739-2022).

Title: Short and Long Term Non-Invasive Cardiopulmonary Exercise Assessment in previously Hospitalized COVID-19 Patients.

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Conflict of interest: None

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 multisystemic illness[3,4]. This so-called Post-Acute Sequelae of SARS-CoV-2 infection (or 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 categorized into two clinical entities. The first being 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 cardio-pulmonary 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.* reported on non-invasive treadmill CPET findings in previously hospitalized COVID-19 patients at 3- and 12-months following discharge in a prospective, longitudinal, multicenter study. The study population was accrued from 6 different institutions across Norway and consisted of a heterogenous population of post-COVID-19 patients, including 20% who required intensive care unit (ICU) 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 VO_2 ≤80% predicted). The authors concluded that amongst those with depressed peak VO_2 at months 3 and 12, nearly half (48%) were "deconditioned". The remainder of patients with reduced peak VO_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 VO_2. While there was interval improvement in peak VO_2, aerobic exercise capacity at the anerobic threshold (AT), and peak O_2 pulse at 12 months, previously hospitalized COVID-19 patients report persistent dyspnea (on BORG CR 10 scale) and exhibit depressed peak VO_2 when compared to age and sex-matched controls[12]. At 3- and 12-months, approximately 14% and 22% of patients, respectively underwent rehabilitation. Whether or not rehabilitation program objectively improved the peak VO_2 in this sub-group of patients was not reported.

The authors are to be commended on the execution of this multicenter 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 one-year following hospitalization. However, like prior non-invasive CPET studies, the current study by *Ingul et al* does not offer a comprehensive patho-physiological rationale for the persistent exertional intolerance experienced by these patients[13]. Specifically, without invasive hemodynamic data and blood gas analysis, the authors were not able to examine if their previously hospitalized post-COVID-19 patients experienced a primary peripheral limit to exercise characterized by impaired systemic O_2 extraction (EO_2)[6,8].

According to the FICK principle, in the absence of a pulmonary mechanical limitation, reduced peak VO_2 is the result of a blunted cardiac output (CO) response, impaired systemic EO_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 VO_2 was limited primarily by impaired systemic EO_2 when compared to age- and sex-matched controls[6]. Importantly, this disparity was evident despite a peak heart rate response and O_2 delivery (DO_2) that was similar

between both post-COVID-19 and control subjects. All 10 patients did not require hospitalization, and none had abnormalities evident on chest CT imaging, PFT, or resting echocardiogram, and all had normal hemoglobin levels. In the current study by *Ingul et al*, deconditioning was defined as a peak VO_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 O_2 pulse, and normal or low VO_2 at AT). With the myriad of non-invasive CPET parameters required to fulfill its definition, deconditioning remains a diagnosis of exclusion. Although patients who are deconditioned can exhibit impaired EO_2 with exercise[14], 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 programs by the time of their iCPET.

It is worth noting the close overlap between the clinical presentation, iCPET findings, and peripheral neuro-vascular dysregulation observed in PASC and myalgic encephalitis/chronic fatigue syndrome (ME/CFS)[7,15,16]. Impaired systemic EO_2 and small fiber neuropathy have been both observed in PASC and ME/CFS[16-19]. Furthermore, the causal hypothesis of ME/CFS has also been linked to preceding infection including respiratory viruses[20,21]. This close clinical and neuro-pathophysiological association between PASC and ME/CFS warrants further exploration. In the current study by *Ingul et al*, the average peak VO_2 at 3- and 12-months in hospitalized post-COVID-19 patients were preserved (i.e., peak VO_2 ≥80% predicted) and 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, and 85 patients continued to report of dyspnea at 12 months. In ME/CFS patients with persistent exertional intolerance, there can be a disconnect between a “normal” peak VO_2 (i.e., peak VO_2 ≥80% predicted) and a supra-normal CO (e.g., on average peak CO is approximately 100% predicted)[16]. In this pathophysiological scenario, the reduced peak VO_2 relative to the supra-normal CO with preserved DO_2 is a function of an impaired systemic EO_2[16]. It is therefore plausible that in the current study by *Ingul et al*, the persistent dyspnea experienced at 12 months despite interval improvement in peak VO_2 maybe the consequence of persistently impaired systemic EO_2. One possible explanation for the impaired systemic EO_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 fiber neuropathy[16] while a recent study suggested a potential role of mitochondrial dysfunction in PASC patients[22].

The COVID-19 pandemic has led to a dramatic loss in 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 hospitalization rates have been mitigated with the advent of vaccines[23] and various acute pharmacotherapeutic options[24-27]. However, for the patients with PASC, their ongoing symptomatology persists and may even have implications beyond exercise intolerance[28]. While the interval improvement in aerobic exercise capacity reported in the study by *Ingul et* al offers some reassurance, future studies focused on accurate cardio-pulmonary-systemic vascular hemodynamic assessment coupled with advanced -omics molecular phenotyping is warranted to help better understand the patho-mechanistic process that begets PASC so help develop therapeutic options for our patients.

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