Phenotyping long COVID

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Patients who recover from an acute SARS-CoV-2 infection often present with persistent symptoms lasting for months. The cardiopulmonary exercise test profile of those with "long COVID" is suggestive of deconditioning with a tendency to hyperventilation. https://bit.ly/3y8n0Bt

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The public health consequences of the epidemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections may well go beyond the current burden on hospital services and the indirect effects of social distancing and lockdowns. Patients, particularly older ones with comorbidities, experience persistent dyspnoea, fatigue, body aches and brain fog for months after the acute phase of coronavirus disease 2019 (COVID-19) [1]. Post-acute sequelae of SARS-CoV-2 infection, more commonly called "long COVID", attract considerable media attention, patient advocacy group-initiated research and, recently, USD 1.15 billion of funding by the US National Institutes of Health (NIH) [1]. Cellular damage, inflammatory cytokine production and pro-coagulant state induced by SARS-CoV-2 infection provide a pathophysiological rationale for long-lasting symptomatology [2]. Given the magnitude of the COVID-19 pandemic, with currently over 150 million reported cases, long COVID may emerge as a huge worldwide medical problem [1, 2].

Long COVID is defined by the persistence or development of symptoms beyond 4 weeks from the onset of the disease, when testing for replication-competent SARS-CoV-2 has been negative for at least 1 week [2]. Its epidemiology remains incompletely understood. The numbers vary from one study to another, depending on methodology, whether patient- or hospital-initiated surveys are used, structure of follow-up programmes, comorbidities, and length of hospital stay, with or without intensive care unit (ICU) stay. Several North American and European studies report an incidence of long COVID of 30 to 90% at 6 months [2].

In the first reported long COVID study, on 134 patients followed by a post-acute outpatient service in Rome, Italy, only 13% were free of symptoms after 2 months [3]. The most common complaints were fatigue (53%), dyspnoea (43%) and joint pain (27%) [3]. In a large prospective cohort study from Wuhan, China on 1733 patients evaluated after a median of 6 months, 76% reported at least one of a list of 17 symptoms, the three most common being fatigue and muscular weakness (63%), sleep difficulties (26%), and anxiety or depression (23%) [4]. Lung function and chest imaging in a subgroup of 390 of these patients showed a 6-min walk distance below the lower limit of normal in 24–29%, a lung diffusing capacity for carbon monoxide (D_{LCO}) below 80% predicted in 29–56% and abnormal chest computed tomography (CT) imaging in 41–45% (mainly ground glass opacities and irregular lines suggestive of fibrotic changes). However, none of these findings was correlated to symptoms. A third of 134 patients reported in a smaller Belgian study still complained of fatigue and/or dyspnoea despite only mild impairment of their lung function and an almost complete normalisation of chest CT lesions after 6 months [5]. The authors also underscored the apparent discrepancy between the presence/absence of dyspnoea and chest CT imaging or lung function tests. Similar results were reported in 103 patients at 3 months following discharge from six Norwegian hospitals [6]. Dyspnoea limiting daily activities was present in two thirds of the patients, but unrelated to chest CT opacities or reduced $D_{LCO,}$ which were noted in a

quarter of the patients. In a most recent Chinese study on 83 patients evaluated every 3 months up to 1 year, dyspnoea scores, exercise capacity assessed by a 6-min walk distance, D_{LCO} and forced vital capacity improved over time, along with a decreased incidence of abnormal chest CT findings from 78% at 3 months to 27% of at 6 months [7].

Unique to the COVID-19 pandemic has been the role of patient advocacy groups finding one another through Twitter and other social media in identifying persistent symptoms and influencing research and clinical attention [8]. Surveys conducted by these groups have helped to identify persistent symptoms such as brain fog, fatigue and body aches as important components of long COVID. But patient-driven research is inevitably associated with methodological uncertainties. For example, of the 3762 respondents of an online survey published by the highly influential Body Politic COVID-19 Support Group (www.wearebodypolitic.com/covid19), a mere 600 or 15% had tested positive for the virus at any time. Another concern is the important overlap with post-traumatic syndromes and depression [4], which are as always associated with breathlessness, myalgia, anorexia and confusion [9, 10]. Similar incidences of post-traumatic syndromes, depression and anxiety has been previously reported in survivors of SARS or Middle East respiratory syndrome (MERS) [11].

Yet respiratory symptoms dominate both the acute phase and longer-term sequelae of COVID-19, and exercise dyspnoea and fatigue are the most common complaints. Accordingly, three cardiopulmonary exercise testing (CPET) studies in long COVID patients reported in this issue of the *European Respiratory Journal* are timely and deserve particular attention.

The first study by Rinaldo *et al.* [12] reports on 75 patients evaluated 3 months after a hospital stay with critical (n=39), severe (n=18) and mild to moderate disease (n=18). 46 of the patients still complained of dyspnoea during daily activities, and 43 showed residual parenchymal impairment at high resolution chest CT. Spirometry was within predicted normal range but D_{LCO} was mildly decreased at mean±SD 71±14% predicted. Maximum oxygen uptake (V'_{O_2max}) was 20 mL·kg^{-1}·min^{-1} (83±15% pred), the anaerobic threshold at 54% of peak V'_{O_2max} and the slope of ventilation to carbon dioxide output (V'_E/V'_{CO_2}) 28±3, with a preserved breathing reserve >15% of maximum voluntary ventilation in all the patients. The V'_{O_2} *versus* work rate slope was on average normal at 10 mL·W^{-1} and peak heart rate on average limited at 141 bpm. According to the authors, this CPET profile was suggestive of deconditioning with no argument in favour of a cardiac or a ventilatory limitation to exercise capacity. Interestingly, there were no correlations between V'_{O_2max} and lung function tests, including D_{LCO} or chest CT findings.

The second study by Skjørten *et al.* [13] prospectively examined 189 patients 3 months after discharge from six Norwegian hospitals. After exclusion of 26 of the patients with background chronic lung or cardiovascular disease and seven patients with inconclusive submaximal CPET, half of the remaining still suffered from shortness of breath in daily activities. Spirometry was in the normal range, but D_{LCO} was mildly decreased. V'_{O_2max} was 29±8 mL·kg^{-1}, the anaerobic threshold at 52% of V'_{O_2max}, and the V'_E/V'_{CO_2} slope at 28±5 with a preserved breathing reserve at 30±17%. Oxygen pulse was preserved at 15 ±4mL and maximum heart rate limited to 157±20 bpm. V'_{O_2max} was lower in the patients with previous ICU stay or with persistent dyspnoea. Ventilation, breathing reserve, and V'_E/V'_{CO_2} slope were not different between the ICU and non-ICU groups. These CPET data again suggested deconditioning as a predominant cause of dyspnoea/fatigue symptomatology.

The third study by Motiejunaite *et al.* [14] reports on 114 patients evaluated 3 months after hospital discharge. Median values of V'_{O_2max}, maximum O_2 pulse and V'_E/V'_{CO_2} slope were 18 (interquartile range 15–21) mL·kg^{-1}·min^{-1}, 10 (8–12) mL and 33 (30–38), respectively. The authors insisted on the contribution of increased V'_E/V'_{CO_2}, which was higher than the upper limit of normal of 35 in a quarter of the patients, to exercise dyspnoea, but otherwise confirmed a deconditioning CPET profile with lower V'_{O_2max} than in other studies, tentatively explained by comorbidities and more severe initial disease.

These results are in agreement with those of eight previous, mostly smaller, studies on a total of 203 patients [15–22]. When grouped together thus on a total of 581 patients, mean values of forced expiratory volume in 1 s of 97% predicted, D_{LCO} of 83% predicted, V'_{O_2max} of 82% predicted with an anaerobic threshold of 50% of V'_{O_2max}, V'_E/V'_{CO_2} slope of 30, preserved breathing reserve and moderately decreased maximum heart rate, altogether offer a CPET profile of deconditioning on the recovery of an acute inflammatory process, prolonged bed rest, and post-traumatic syndrome and depression. Interestingly, there was a tight correlation (r^2=0.92, p<0.01) between V'_{O_2max} (in % predicted) and length of hospital stay as calculated on a total of 298 patients from four studies [13, 15, 16, 20]. In one of the studies, CPET was combined with exercise stress echocardiography [21]. The results excluded right heart dysfunction or

exercise-induced pulmonary hypertension as another possible cause of exercise limitation, but uncovered a decreased O_2 extraction by the exercising muscle compatible with severe deconditioning.

Several studies have attempted subgroup analyses of patients presenting with CPET or lung function variables below or beyond limits of normal in % predicted. However, in the presence of mean values well within or only at the limit of normal, this may be misleading as a significant proportion of the reported patients presented with comorbidities such as obesity, cardiovascular conditions and chronic lung diseases, which increased the noise on the reported measurements. This was only partly corrected for by a somewhat less than healthy control population by SKJØRTEN *et al.* [13]. Instead of referring to limits of normal determined on healthy or near-healthy populations, comparing with age-, sex-, social environment- and comorbidity-matched controls is more appropriate. Until now, 76 long COVID patients have been compared to only 49 matched controls reported in only two studies [15, 21]. More is needed.

How does long COVID compare with other post-critical respiratory illnesses? In a 1-year follow-up study of 117 patients who recovered from acute respiratory distress syndrome (ARDS) as a result of a variety of causes, including sepsis, pancreatitis, pneumonia and trauma, lung volume and spirometric measurements were normal by 6 months, but D_{LCO} remained low throughout the 12-month follow-up [23]. Quality of life questionnaires and exercise capacity assessed by 6-min walk distances improved during the 12 months of follow-up but remained lower than normal. The absence of systemic corticosteroid treatment, the absence of illness acquired during the ICU stay, and rapid resolution of lung injury and multi-organ dysfunction were associated with better functional status during the 1-year follow-up. In a study of 50 ARDS patients ventilated for more than a week, CPET performed 1 month after hospital discharge showed, according to the authors, a "multifactorial" limitation of exercise capacity, but with deconditioning and muscle weakness as major contributory factors, and no ventilatory limitation [24].

A similar picture emerged from follow-up studies in SARS survivors, with decreased quality of life, decreased exercise capacity but a unspecific CPET profile suggestive of deconditioning, persistent chest CT abnormalities in about half of the patients and, importantly, a disconnect between imaging sequelae, lung function tests and dyspnoea/fatigue symptoms [25]. A CPET profile of severe deconditioning with, interestingly, higher than normal V'_E/V'_{CO_2} slope, is reported after respiratory insufficiency requiring mechanical ventilation [26]. It is important to note that quality of life questionnaires and 6-min walk tests improved over time in studies with repetitive assessments during a 1-year follow-up of either any cause ARDS [23] or SARS [25]. A similar evolution has now been reported in long COVID patients [7].

Follow-up studies on COVID-19 patients report on persistently abnormal biology with increased markers of inflammation, or abnormal magnetic resonance imaging suggesting on-going inflammation or scarring of the heart and the brain [13, 27, 28]. Whether this similarly occurs in the aftermath of ARDS, SARS or MERS is not known. However, some complaints such as loss of olfaction or persistent cough may be more typical of long COVID, and related to persistently increased inflammatory markers, as would be depression/fatigue symptoms [27, 28]. Furthermore, a minority of patients recover but with persistent anaemia, hypoxaemia or CPET suggestive of decreased ventilatory reserve or impaired cardiac responses. Exercise testing is important for the identification of these patients who may need more thorough diagnostic procedures and attentive follow-up with rehabilitation.

Studies with more comprehensive CPET may be needed allow for a better understanding of long COVID. Combining CPET with right heart catheterisation or cardiac imaging may uncover exercise pulmonary hypertension, uncoupling of the right heart from the pulmonary circulation or altered matching of convective and diffusive O_2 transport mechanisms [29]. Such analyses were recently reported in patients with chronic thromboembolic pulmonary hypertension [30] or heart failure [31]. There is an intriguing tendency to exercise hyperventilation in long COVID [13, 14], which may relate to persistent lung thrombotic or fibrotic changes, anaemia, hypoxaemia or altered chemosensitivity. This will require further exploration with arterial blood gases analysis and V'_E/V'_{CO_2} *versus* P_{CO_2} diagrams will be needed for the differential diagnosis between increased dead space and chemosensitivity [32].

Long COVID remains an enigma. Three potential pathophysiological mechanisms include virus-specific pathophysiological changes, immunological aberrations and inflammatory damage in response to the acute infection and expected sequelae of post-critical illness [2]. At this stage, there has not been any reports of typical biological or lung function test results, or chest or brain imaging profile. The reports by RINALDO *et al.* [12], SKJØRTEN *et al.* [13] and MOTIEJUNAITE *et al.* [14] do not disclose a long COVID-specific standard CPET profile either.

We agree with a recent editorial in this journal that a better understanding of the mechanisms, predisposing factors and evolution (after 6 months) of long COVID will require broad international cooperation, in order to offer efficacious preventative and curative approaches [33]. We argue that unambiguous phenotyping with use of comprehensive CPET will have to be part of it. In this respect, the studies by Rinaldo *et al.* [12], Skjørten *et al.* [13] and Motiejunaite *et al.* [14] are important steps in the right direction, but there still is a long way to go.

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