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Deconditioning in COVID-19 survivors with reduced exercise performance: A role for endothelial dysfunction?

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ABSTRACT

Recent studies have reported an impaired exercise response at cardiopulmonary exercise testing (CPET) during convalescence from coronavirus disease 2019 (COVID-19). In detail, these previous reports suggest the presence of functional limitations in a consistent proportion of COVID-19 survivors, in the absence of relevant alterations of ventilatory and gas exchange parameters at CPET. Therefore, deconditioning has been proposed as the main mechanism of the reduced peak oxygen uptake in this clinical setting. This interpretation of the results is supported by the evidence that deconditioning is a recognized aspect of the post-intensive care syndrome, with acute sarcopenia being frequently observed among COVID-19 survivors. Here, we hypothesized the role of endothelial dysfunction as a key pathogenic mechanism of the functional limitations of COVID-19, including multisystem deconditioning and subsequent exercise intolerance.

Short communication

Among a number of clinical manifestations of the coronavirus disease 2019 (COVID-19), an impaired exercise response has been reported at cardiopulmonary exercise testing (CPET) during convalescence. Thus, the European Respiratory Society/American Thoracic Society task force recommended CPET in the follow-up of all COVID-19 patients [1]. Given the number of functional limitations of the post-acute phase, a better understanding of the mechanisms underlying the reduced CPET performance would allow for the implementation of more effective personalized approaches and rehabilitation strategies.

In a recent paper RINALDO et al. prospectively evaluated exercise capacity in 75 COVID-19 survivors with critical (n = 39, 52.0%), severe (n = 18, 24.0%) or mild-moderate disease (n = 18, 24.0%) [2]. A reduced CPET performance, as expressed by a peak oxygen uptake (VO$_2$) $< 85\%$ of predicted, was documented in 34 patients (54.7%). Of interest, patients with a reduced exercise capacity showed an early anaerobic threshold, with no alteration of parameters of ventilatory efficiency and gas exchange. Thus, the authors concluded that deconditioning is the main mechanism of the reduced exercise response in their study population.

This is an interesting finding, in line with that of a more recent study on a similar patient population, reporting an almost identical proportion of patients with impaired CPET performance (54.3%), with general deconditioning being the most common limiting factor [3]. Accordingly, extrapulmonary factors were identified as the main reason for exercise limitation in one of the first reports on CPET in a small case-series of 10 moderate-to-severe COVID-19 survivors [4]. The key role of physical deconditioning is confirmed also in the largest study currently available on this issue (n = 156), which however reports only a one-third rate of reduced exercise capacity, likely due to the less severe disease course in that patient group [5].

Overall, in line with current evidence, RINALDO et al. suggest the absence of relevant functional sequelae on ventilatory and gas exchange response to exercise in COVID-19 survivors. Moreover, they hypothesize that deconditioning might be related to a direct effect of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the muscle as well as to a prolonged hospital stay and post-hospitalization syndrome.

We share this interesting interpretation of their results, supported by the evidence that deconditioning is a recognized aspect of the post-intensive care syndrome, with acute sarcopenia being frequently observed among COVID-19 survivors [6]. Here, we want to highlight the hypothesis that endothelial dysfunction may play a pathogenic role in determining the functional limitations of the post-acute phase of COVID-19, including multisystem deconditioning and subsequent exercise intolerance.

Endothelial dysfunction is the common pathogenic background of most manifestations of COVID-19, thus leading the European Society of Cardiology to recommend its clinical assessment in the follow-up of COVID-19 survivors. A dysfunctional endothelium has been identified as a key determinant of sarcopenia and muscle weakness in different clinical settings, including COVID-19. In detail, it can be hypothesized that endothelial damage due to direct or indirect viral action is associated with a procoagulant state and subsequent formation of microthrombi, resulting in multiorgan dysfunction and muscle damage [7]. Moreover, a dysfunctional endothelium is associated to a lower nitric oxide (NO) bioavailability, which is responsible for an impaired smooth muscle cells relaxation and reduced vasodilation [8]. Overall, these pathological mechanisms may lead to a lower blood and oxygen (O$_2$) supply to the periphery, thus determining muscle weakness and acute

Abbreviations: COVID-19, coronavirus disease 2019; CPET, cardiopulmonary exercise testing; VO$_2$, peak oxygen uptake; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NO, nitric oxide.
sarcopenia. On the other hand, the presence of a primary myopathy in COVID-19 patients cannot be ignored, with impaired peripheral O\textsubscript{2} utilization or extraction due to mitochondrial injury.

However, skeletal muscle involvement is only one aspect of deconditioning, which is a systemic adaptation to a less demanding environment. While basal shear-rate appears enhanced in large arteries by acute physical inactivity, bed-rest conditions seem to decrease shear stress at a microcirculatory level, and a chronic decrease in shear stress is able to induce endothelial apoptosis and dysfunction. Microcirculatory endothelial dysfunction can also participate in cardiovascular and autonomic deconditioning, determining changes in energy metabolism and organ perfusion [9]. However, endothelial dysfunction may be also a consequence of inactivity and, most important, it has been demonstrated that a regular physical activity is able to improve endothelial function by increasing phosphorylation of endothelial NO synthase [10].

Overall, the complex interplay between exercise and endothelial function is still a matter of study, and it should be taken into account during periods of prolonged deconditioning. In line with current evidence, endothelial function testing should be considered in the follow-up of COVID-19 patients, thus contributing to the identification of personalized exercise-based rehabilitation strategies.

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**Declaration of Competing Interest**
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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