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Mechanisms of exercise intolerance after COVID-19: new perspectives beyond physical deconditioning

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The long-COVID-19 or post-COVID-19 syndrome is defined as the persistence of symptoms after four weeks of viral infection onset, in the absence of viral replication for 3 weeks.[1] Several studies have shown that approximately 60-70% of patients report persistence of symptoms for weeks to months after acute presentation. The primary symptoms include fatigue/muscle weakness, dyspnea, depression/anxiety, and sleep and cognitive disturbances. It remains unknown why several COVID-19 patients develop chronic symptoms following the acute event. Moreover, it seems that these chronic symptoms do not correlate well with the severity of the acute clinical presentation.[2,3] The main hypotheses to explain these findings relate to the viral toxicity itself, changes in the immune system, systemic inflammatory response, endothelial and microvascular injury and/or microthrombi, fibroblast proliferation due to diffuse alveolar damage, in addition to mechanical stretch from ventilation, medications (corticosteroids, neuromuscular blockers, etc.), prolonged hospitalization with immobility, and post-traumatic stress syndrome.

Considering this scenario, it would be expected, from a pathophysiological standpoint, that those patients would demonstrate reduced exercise tolerance with decreased aerobic capacity. However, according to the literature, few studies have investigated the role of cardiopulmonary exercise testing (CPET) in COVID-19 (Table 1). Based on those studies, it has been suggested that exercise intolerance could result from physical deconditioning.[4-6] But what is physical deconditioning? In the medical dictionary, it is defined as the "loss of physical fitness due to the inability to maintain an optimal level of physical activity or training. Inactivity for any reason can lead to deconditioning." Regarding CPET findings, physical deconditioning can be described as the reduction of peak VO_2 with or without slight tachycardia in the absence of known central and peripheral cardiocirculatory diseases. The presence of an early lactate threshold, for example, is only found in individuals without central cardiocirculatory diseases who are extremely sedentary and with high muscle impairment due to inactivity, as is the case of patients with debilitating chronic diseases.

In terms of the evaluation of exercise intolerance mechanisms by CPET, it is important to define whether the effort limitation is due to a central or peripheral cardiocirculatory origin and whether there is a ventilatory or gas exchange limitation alone or associated. Exercise limitations of central cardiocirculatory origin, for example, can occur even in the presence of normal cardiac exams at rest and can be related to low O_2 delivery. Considering the hypothetical presence of myocarditis and endothelial/pulmonary microvascular lesions in the acute phase of COVID-19 infection, the exercise limitation in the post-COVID-19 syndrome related to central cardiovascular origin could be due to chronic inflammatory myocardial lesions - the prevalence of clinical and subclinical myocarditis in college athletes was 2.3% by cardiac MRI and may be one of the reasons for reduced performance in this population[7] - or pulmonary microvascular lesions. Pulmonary vascular disease, detected exclusively under physical stress, is also called exercise pulmonary hypertension'. In addition to cardiac pump impairment, the delivery of O_2 could also be compromised by reduced O_2 transport due to anemia, especially after discharge.[8]

From the peripheral standpoint, exercise intolerance may be due to impaired peripheral O_2 utilization or reduced peripheral O_2 extraction due to mitochondrial injury, with a consequent negative impact on energy production during cellular respiration for ATP formation. In keeping with this, Baratto et al.[8] demonstrated that post-COVID-19 patients at hospital discharge had a higher cardiac output (CO) at rest, lower arterial O_2 content (reduced convective O_2 transport), and a lower arteriovenous O_2 difference compared to healthy controls, but with similar O_2 extraction. During exercise, despite the higher CO, post-COVID-19 patients had lower muscle O_2 extraction in the absence of increased pulmonary artery pressure and pulmonary vascular resistance, justifying the lower peak VO_2.[8] When evaluating patients with persistent symptoms after COVID-19 infection, Singh et al.[3] elegantly demonstrated, through invasive CPET, that O_2 delivery was normal and associated with reduced peripheral O_2 extraction and elevated mixed venous O_2 saturation compared to controls, resulting in reduced peak VO_2, indicating lower diffusive O_2 delivery to the mitochondria.[3] In their study, none of the patients presented central cardiocirculatory limitations. Corroborating with peripheral muscle impairment due to mitochondrial cellular respiration dysfunction, and not to peripheral muscle deconditioning, a recent case report with muscle biopsy performed after 3 weeks of mild COVID-19 infection evidenced a reduced actin:myosin ratio with loss of myosin filaments, thus confirming the presence of primary myopathy by COVID-19 as a cause of chronic fatigue.[9] These findings open a

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new perspective that suggests that myopathy due to viral injury might be responsible for the persistence of fatigue in long-COVID-19. Similarly, it is hypothesized that these patients may develop post-viral myalgic encephalomyelitis/chronic fatigue syndrome with possible associated small-fiber neuropathy, as previously described in other viral infections, or damage to olfactory sensory neurons, causing reduced cerebrospinal fluid flow, with congestion of the glymphatic system and subsequent toxic accumulation in the central nervous system.[10,11]

Reduced peak VO_2 has not been the only finding described in post-COVID-19 syndrome. Some studies have reported mild hyperventilation due to an increase in the minute ventilation to carbon dioxide output ratio ($V'E/V'CO_2$) during exercise, which could be justified by an increase in central chemosensitivity[3] or by dysfunctional breathing,[5,6] which would reduce the arterial CO_2 pressure by increasing the ventilatory drive. It is noteworthy, however, that systemic stimuli of ventilation, such as activation of metabo- and mechanoreceptors during exercise, present in the peripheral muscles, can also justify the increase in $V'E/V'CO_2$ in the absence of pulmonary and cardiac sequelae.[3] Another possible cause for ventilatory inefficiency would be the increase in dead space as a fraction of tidal volume (VD/VT), which may be present in patients with endothelial and/or microvascular injury, poor alveoli perfusion, and/or destruction of the pulmonary vascular bed in fibrotic areas, associated with reduced O_2 diffusion through the blood-alveolar barrier.[3,8] This hypothesis would be plausible to justify, for example, the hypothetical presence of exercise pulmonary hypertension (not confirmed so far in the literature).[3,8] The VD/VT could also be elevated as a consequence of the reduction in VT during exercise due to the persistence of interstitial pulmonary fibrosis with consequent changes in ventilatory mechanics and ventilatory limitation, with possible associations with the extent of acute interstitial pulmonary involvement.[12] Finally, the presence of effort-induced hypoxemia could reduce muscle O_2 delivery, causing limitations in gas exchange.[5]

Thus, considering the current pathophysiological knowledge of intolerance mechanisms and the range of systemic manifestations of the acute phase of COVID-19 infection, it would be simplistic for us to consider that all chronic symptoms of the long-COVID-19 syndrome

Table 1. Summary of the main studies evaluating exercise intolerance in patients after COVID-19 infection.

Time of evaluation sample (n)	Dyspnea (mMRC)	Subgroups	Peak VO_2 in the sample	Findings
Rinaldo et al.[2] 3 months (n = 75)	57%	Severity of hospitalization: mild-moderate, severe, and critical	54% (VO_2 < 85%prev) (*post hoc* analysis)	Older Greater residual pulmonary sequelae No difference in lung function No difference in peak VO_2 in cardiocirculatory and gas exchange responses. Mild increase of $V'E/V'CO_2$ in the critical *vs.* mild-moderate group
Rinaldo et al.[4] 3 months (n = 75)	52%	Reduced or normal peak VO_2	55% (VO_2 < 85%prev)	Lower lactate threshold Lower $\Delta VO_2/\Delta WR$ Lower pulse O_2
Skjørten et al.[5] 3 months (n=156) (multicenter)	47%	Comparison with normal population without COVID-19 by z-score (20% in ICU)	89 ± 17%prev 31% (VO_2 < 80%prev)	15% reduced lactate threshold 16% ventilatory limitation 23% desaturation >4% 15% increased $\Delta V'E/\Delta V'CO_2$
Motiejunaite et al.[6] 3 months (n = 114)	Dyspnea 40% Fatigue 32%	DCO ≤ or > 75%prev	75% (VO_2 < 85%prev)	Smallest peak VO_2 Lower lactate threshold Tendency to greater limitation to exercise
Liu et al.[12] 7 months (n = 41)	-	Persistence or absence of pulmonary fibrosis on chest CT	16.4 ± 3.6 mL/kg/min (with fibrosis) 20.2 ± 3.7 mL/kg/min (no fibrosis)	Older and more severe hospitalization Smallest peak VO_2 Lower METS Higher $V'E/V'CO_2$
Debeaumont et al.* 6 months (n = 23)	78%	ICU *vs.* ward	52% (VO_2 < 85%prev)	Higher $\Delta V'E/\Delta V'CO_2$
Dorelli et al.** 5 months (n = 28)	-	$\Delta V'E/\Delta V'CO_2$ > 31 or ≤ 31	29.2 ± 8.3 mL/kg/min	No difference in pulmonary function variables at rest and in CPET responses

Abbreviations: mMRC: Medical Research Council modified dyspnea scale; peak VO_2: peak exercise oxygen consumption; WR: work rate; $V'E/V'CO_2$: minute ventilation by carbon dioxide output; DCO: carbon monoxide diffusion; chest CT: chest computed tomography; ICU: intensive care unit. *DOI:https://www.doi.org/10.1093/ptj/pzab099 **DOI: https://www.doi.org/10.3390/diagnostics11030507.

are due to physical deconditioning by inactivity or prolonged hospitalization. The physical deconditioning theory does not explain the presence of persistent symptoms in patients who were affected by mild forms of the disease, many of whom did not even require hospitalization. Similarly, this theory does not explain the dissociation between the severity of hospitalization and the reduction in peak VO_2 reported so far, nor does it explain the antagonism of the persistence of symptoms in patients with preserved peak VO_2.[4-6]

In light of the potential complexity and the lack of knowledge on the post-COVID-19 syndrome, it is unacceptable to be simplistic when attempting to unravel the post-COVID-19 syndrome exercise intolerance mechanisms. More robust scientific evidence is needed before drawing simple conclusions.

AUTHOR CONTRIBUTIONS

EVMF and RKFO: preparation, writing, and revision of the manuscript.

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