Letters to the Editor

Cardiopulmonary exercise test in patients with post SARS-CoV-2 sequelae: need to create a multicenter working group

Prueba de esfuerzo cardiopulmonar en pacientes con secuelas tras el SARS-CoV-2: necesidad de crear un grupo de trabajo multicéntrico

To the Editor,

We read with attention and enjoyment the study by Ramírez-Vélez et al.[1] In the study, the authors analyzed in detail the ventilatory response during exercise testing with oxygen uptake in a population of patients with symptoms compatible with long COVID-19. The results of the study confirmed that ventilatory inefficiency played an important role in post-COVID-19 sequelae, but did not explain the role of deconditioning and obesity.

Ramírez-Vélez et al. used a control group of patients who had not had SARS-CoV-2. In the control group, there was a significantly lower proportion of patients with obesity (29% vs 10%; $P = .006$) and the patients were significantly more active (physical activity, 983 vs 1732 MET/min/wk; $P < .001$). In the study, they observed a significant abnormality in the ventilatory efficiency data in the subgroup of patients with long COVID-19 and hypothesized that the excess adiposity and low physical activity levels could, in part, explain the findings of the study. A subgroup analysis was not performed (eg, patients with vs without obesity, previously active vs inactive) nor were there any data from static respiratory function tests.

In line with the findings reported by Ramírez-Vélez et al., many studies,[2] including that by our group,[3] have described ventilatory inefficiency as one of the key abnormalities in oxygen uptake testing in patients with post-SARS-CoV-2 sequelae. In most of the studies, ventilatory inefficiency does not explain the symptoms in all patients. In a study by Singh et al., using cardiopulmonary exercise testing along with cardiac catheterization, the authors demonstrated that persistent dyspnea in patients without post-COVID-19 cardiopulmonary sequelae was secondary to abnormalities in peripheral oxygen extraction mechanisms, mainly due to reduced oxygen diffusion in the tissue microcirculation.[4] The hyperventilation was explained in this study as secondary to a shift in peripheral muscle fibers, to a predominance of group III/IV fibers, which are essential in the regulation of ventilation.

When interpreting the results of oxygen uptake testing, it is essential to have spirometry results, possibly along with a diffusion test and calculation of carbon monoxide diffusion. We noted the lack of 2 parameters that, in our opinion, are essential for interpreting the results, namely dead space behavior during exercise and respiratory reserve. This information, along with static pulmonary function tests, allows us to refine the diagnosis against other conditions such as pulmonary hypertension, pulmonary thromboembolism, psychogenic hyperventilation, and obstructive or restrictive pulmonary disease.

Another important point in oxygen uptake testing is the use of a suitable protocol that allows tolerance of maximum exertion before reaching muscular exhaustion. The protocol used in this study, using a ramp, starting at 25 W and with 25-W increments every 2 minutes, may have been poorly tolerated by patients with lower fitness levels and with symptoms of chronic fatigue. We therefore would have liked the authors to use protocols adapted to each patient that would allow the test to be completed in 8 to 12 minutes, thus ensuring better exercise tolerance.

The sequelae of SARS-CoV-2 infection have been compared with those observed in postviral syndromes such as myalgic encephalomyelitis or chronic fatigue syndrome. In many cases, the patients have a very poor workload tolerance. Although rehabilitation based on physical exercise is an essential pillar of the treatment of fatigue, exercise is not always beneficial and it is important to avoid "postexertional malaise".[5]

This represents an important health and social problem that could result in a huge workload with no clear benefits to patients' quality of life, especially if we do not ascertain the pathophysiological mechanisms of COVID-19 sequelae or find effective treatments. Cardiopulmonary exercise testing can provide valuable information to help determine the pathophysiology of the sequelae of SARS-CoV-2 infection. Although hyperventilation is one of the main abnormalities observed with exercise, we do not believe that it explains the symptoms in all patients. Likewise, we cannot risk underdiagnosis of other sequelae of SARS-CoV-2 or worsening of previously undiagnosed diseases. Nonetheless, we are highly enthused at the efforts by Ramírez-Vélez et al. to undertake an in-depth investigation of the pathophysiological mechanisms of SARS-CoV-2 sequelae, and perhaps multicenter working groups can be established to determine as much as possible of the natural history of this complex condition.

FUNDING

No funding.

AUTHORS' CONTRIBUTIONS

The initial idea for the letter came from L. Vannini. A. Quijada-Fumero, A. Laynez-Carnicero, and J. Hernández-Afonso contributed to the writing and editing of the manuscript.

CONFLICTS OF INTEREST

None.

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Available online 15 February 2023

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https://doi.org/10.1016/j.rec.2022.08.017

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https://doi.org/10.1016/j.rec.2022.12.017
1885-5857/

Cardiopulmonary exercise test in patients with post SARS-CoV-2 sequelae: need to create a multicenter working group. Response

Prueba de esfuerzo cardiopulmonar en pacientes con secuelas tras el SARS-CoV-2: necesidad de crear un grupo de trabajo multicéntrico. Respuesta

To the Editor,

We have read with interest the comments by Vannini et al. regarding our scientific letter[1] on ventilatory response during exercise testing in a population of patients with persistent COVID-19 symptoms. We thank the authors for their observations and comments.

In the assessment of oxygen consumption, we understand the relevance of including spirometry data with diffusing capacity for carbon monoxide (D_{LCO}) testing, given that 43% of patients with SARS-CoV-2 sequelae have been reported to have a D_{LCO} of less than 80% of the predicted capacity.[2] We are aware of this limitation in our work and welcome the comment by Vannini et al. on future improvements to our research.

Regarding the absence of a subgroup analysis (eg, obese vs nonobese, or trained vs untrained) in explaining our previous findings,[1] the figure 1 presented again shows that ventilatory inefficiency is independent of nutritional status or physical activity levels. We disagree that the protocol used in our study "may be poorly tolerated by less trained patients with symptoms of chronic fatigue", suggesting adaptations to achieve better exercise tolerance. As previously mentioned,[1] the mean exercise test time was 13.0 minutes and this small difference still preserves the relationship between VO_2, workload, and heart rate during cardiopulmonary exercise testing.

We agree that the pathophysiological mechanisms of COVID-19 sequelae remain uncertain, and we believe that rehabilitation, based on physical exercise, is a mainstay for the treatment of various persistent symptoms, as recently demonstrated.[3] Indeed, this was the motive prompting our study.[4]

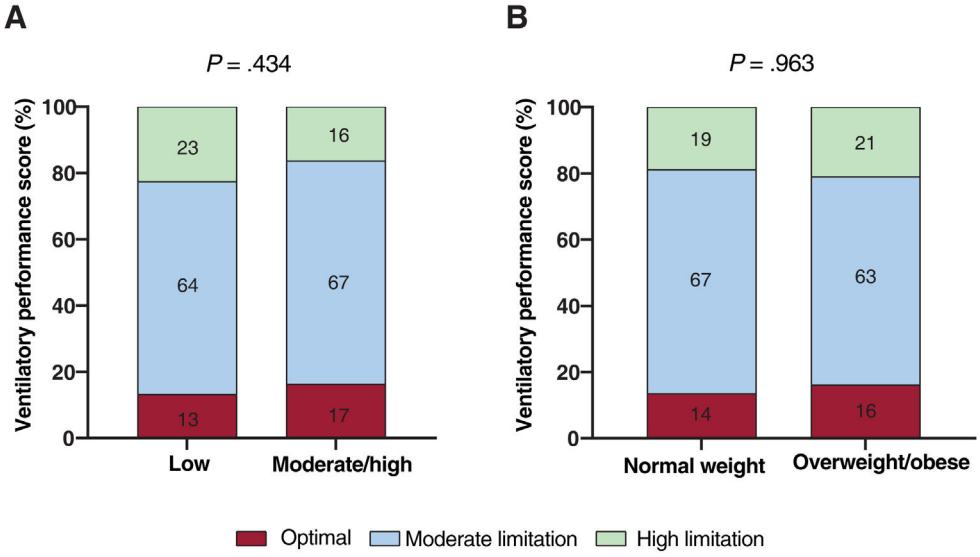

Figure 1. Comparison of physical activity levels (A) and nutritional status by BMI (B) and ventilatory performance categories. The ventilatory performance criteria score is derived from the sum of the abnormal criteria, then classified as follows: no ventilatory limitation (no abnormal criteria), moderate limitation (1-2 abnormal criteria), and high limitation (more than 3 abnormal criteria). Values are expressed as No. (%). Differences were determined using the chi-square contingency test. BMI, body mass index.