



OPEN Impaired pulmonary and muscle function during moderate exercise in female patients recovered from SARS-CoV-2

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This study aimed to assess pulmonary and muscle dysfunction by analyzing the slow component of oxygen uptake ($\text{VO}_{2\text{SC}}$), and mechanical and ventilatory efficiency in adult women recovered from the severe acute respiratory syndrome coronavirus type II (SARS-CoV-2) during a constant load test. 32 women (N = 17 patients with SARS-CoV-2; N = 15 control group) performed two cardiopulmonary exercise tests (CPX) on a cycle ergometer. In the first test, the participants performed incremental CPX until extenuation. In the second test the participants performed a 10-min CPX at a constant load intensity (watts) corresponding to the first ventilatory threshold. There was a 48–72 h rest period between the two tests. There was a significant increase in the $\text{VO}_{2\text{SC}}$ in the patients recovered from SARS-CoV-2 ($160.4 \pm 60 \text{ mL min}^{-1}$) in comparison with the healthy participants ($59.6 \pm 65 \text{ mL min}^{-1}$) ($P < 0.001$). Mechanical efficiency significantly decreased in patients recovered from SARS-CoV-2 compared to the control group ($P = 0.04$). Ventilatory inefficiency significantly increased in the patients recovered from SARS-CoV-2 compared with the control group ($P < 0.001$). Adult women recovered from SARS-CoV-2 infection have important pulmonary and muscular dysfunction and fatigue which contributes to increasing the $\text{VO}_{2\text{SC}}$ and reducing mechanical and ventilatory efficiency during mild-moderate exercise at a constant load.

Multisystemic cardiopulmonary and muscular involvement produces fatigue, pain and muscle weakness as the symptomatology associated with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)^{1,2}. There is an evident female preponderance in the development of fatigue although all patients diagnosed with SARS-CoV-2 will require fatigue screening³.

The assessment of pulmonary oxygen uptake kinetics has been suggested to determine fatigue and a reduced exercise tolerance in cardiovascular and respiratory diseases^{4,5}. Specifically, the pulmonary VO_2 tends to rapidly increase from the onset of exercise until approximately 3 min during prolonged cardiopulmonary exercise test (CPX) at a constant-load. After 3 min, the VO_2 slowly increases for a given production of power, implicating sustained lactic acidosis and surpassing the fundamental component of the beginning of exercise⁶ until a delayed stable state is acquired or maximum VO_2 is reached⁷. This VO_2 response is known as the slow component of VO_2 ($\text{VO}_{2\text{SC}}$)⁶. The evaluation of $\text{VO}_{2\text{SC}}$ has been used as an indicator of the appearance of fatigue limiting exercise tolerance in respiratory diseases^{5,8}.

A key parameter associated with the behavior of the $\text{VO}_{2\text{SC}}$ during exercise is mechanical efficiency (ME), which estimates the effects of alkalization of the blood in gradual loss of muscle efficiency⁶. Patients with reduced ME are less muscularly efficient and can manifest limited capacity for physical activity⁹. The association

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between the $\text{VO}_{2\text{SC}}$ and loss of muscle strength during exercise propose a common physiological mechanism between loss of muscle efficiency and skeletal muscle fatigue¹⁰.

Evaluation of ventilatory efficiency is another relevant parameter in the diagnosis of CPX in cardiorespiratory diseases^{11,12}, essentially to understand the relationship of ventilation (VE) and perfusion in the lungs. Evaluation of the VE and carbon dioxide production slope ($\text{VE} \cdot \text{VCO}_2^{-1}$ slope) is considered as the reference method for predicting mortality, ventilatory inefficiency and exercise tolerance in cardiorespiratory diseases^{11–13}.

The muscle weakness and fatigue experienced in patients recovered from SARS-CoV-2 suggests that marked pulmonary and muscle dysfunction alters $\text{VO}_{2\text{SC}}$ kinetics, reducing ME and increasing ventilatory inefficiency during exercise. However, to our knowledge, this hypothesis has not been scientifically corroborated.

This study aimed to evaluate pulmonary dysfunction and muscle fatigue by analyzing the $\text{VO}_{2\text{SC}}$ kinetics, ME and ventilatory efficiency during a constant-load test on a cycle ergometer in women who have had coronavirus disease 2019 (COVID-19). We hypothesize that the $\text{VO}_{2\text{SC}}$ increases and mechanical and ventilatory efficiency decrease to a greater extent in adult women recovered from COVID-19 compared to healthy adult women during a constant-load test on a cycle ergometer.

Methods

Participants. Seventeen adult women with COVID-19 and fifteen healthy adult women (control group) were recruited for the study. Information on previous medical history was collected. The adjusted morbidity group, which classifies morbidity according to data codified by the health care system, was obtained for all the participants in both groups¹⁴.

In the patients with COVID-19, we collected data related to hospital admission and determined the Acute Physiology and Chronic Health Disease Classification System II (APACHE II) as a predictive system of disease severity and outcome of patients in intensive care units¹⁵. The female patients recovered from COVID-19 included in this study were considered healthy prior to SARS-CoV-2 infection. The main symptoms of female patients recovered from COVID-19 were fatigue and dyspnea. These patients were previously evaluated by the pulmonology, cardiology, and internal medicine services to rule out any type of cardiac or pulmonary pathology that could be the cause of their symptoms (fatigue and dyspnea). To avoid selection bias, patients with any pathology (except COVID-19) that could condition performance in CPX were excluded from the study. The group of healthy adult women did not suffer from any type of disease.

The exclusion criteria were: severe neurological disease, active oncologic disease, neuromuscular and/or orthopedic disorders impeding normal performance of CPX; the absence of signed informed consent.

Inclusion criteria were: age > 18 years; molecular (RT-PCR) diagnosis of SARS-CoV-2 infection; hospitalized and non-hospitalized adult female recovered from COVID-19; healthy adult female who did not have COVID-19 at any time (control group).

The sample size estimation was performed with $\alpha = 0.05$ (5% type I error probability) and $1 - \beta = 0.80$ (80% power). For this study, a total of 15 adult female survivors of COVID-19 were required to detect differences between both experimental conditions.

The study was approved by the Committee of Ethics and Investigation of the hospital (Code: 89/20). The study protocol was performed according to the principles of the Declaration of Helsinki. Written informed consent was collected from all participating women.

Incremental and constant cardiopulmonary test. Prior to the CPX tests, the participants underwent a spirometry test. Patients with COVID-19 performed the incremental and constant CPX on a cycle ergometer with an electromechanical brake (Ergoline900S, Ergoline GmbH, Bitz, Germany). For security reasons, the control group performed the CPX on a cycle ergometer with an electromechanical brake (Ergoselect 100P, Ergoline GmbH, Bitz, Germany). There was a 48–72 h rest period between the two tests. The assessment of patients with COVID-19 was carried out 6–8 weeks after discharge from hospital.

The protocol of incremental CPX until extenuation was performed individualized and adapted to all the participants with gradual increments of 5, 10, 15 or 20 W min^{-1} . In the incremental CPX, the first ventilatory threshold (VT_1) was determined using the method of ventilatory equivalents described by Skinner et al.¹⁶ in which the VT_1 corresponds to an increase of $\text{VE} \cdot \text{VO}_2^{-1}$ without an increase in $\text{VE} \cdot \text{VCO}_2^{-1}$, coinciding with an increase of end-tidal expired partial oxygen pressure (PetO_2).

The protocol of the constant CPX was individualized with 10 min on a cycle ergometer at an intensity corresponding to the VT_1 . The patients were told to maintain a constant similar pedaling cadence (50–80 rpm) in each test. Throughout the whole test the patients underwent continuous 12-lead electrocardiographic monitoring.

An open circuit breath-by-breath Ultima Cardio2 gas analyzer was used for COVID-19 patients (Medical Graphics Corporation, St. Paul, Minnesota, USA) an Ergostik analyzer was used for the control group (Geratherm Respiratory, Bad Kissingen, Germany).

Slow component of VO_2 assessment. During the constant-load test at an intensity of the VT_1 , pulmonary VO_2 kinetics were evaluated. Data of pulmonary VO_2 were registered during 2 min prior to initiation of the constant test (basal status). The basal VO_2 ($\text{VO}_{2\text{B}}$) was considered as the mean during the last 60 s prior to beginning the test. The fundamental kinetics (Phase II) of VO_2 were determined using previously described criteria and were adjusted to a monoexponential function¹⁷: $\text{VO}_2(t) = \text{VO}_{2\text{B}} + \Delta\text{VO}_{2\text{FP}} \times (1 - e^{-(t-\text{TR})/\tau})$, where $\text{VO}_2(t)$ is the value of pulmonary VO_2 at any time t of the VO_2 kinetics; $\text{VO}_{2\text{B}}$ is the of basal VO_2 value; $\Delta\text{VO}_{2\text{FP}}$ is the increase in VO_2 above the baseline reference values and determines the width of the fundamental phase, and τ is the constant of time of the fundamental phase. TR is the time delay. The exponential region of each participant was indi-

	CG	SARS-CoV-2	p-value
Age (years)	45.7 (7.1)	46.4 (12.6)	0.841
Weight (kg)	65.3 (13.5)	74.5 (15.5)	0.061
Height (m)	1.6 (0.1)	1.6 (0.1)	0.224
BMI (kg min ⁻²)	24.9 (5.8)	29.4 (5.9)	0.008
Adjusted morbidity groups (%)			
Basal risk	100%	29.4%	
Low risk	0%	41.2%	
Moderate risk	0%	17.6%	
High risk	0%	11.8%	
Very high risk	0%	0%	
FVC (L)	3.6 (0.3)	3.2 (0.7)	0.088
FVC (%)	100.5 (11.1)	86.4 (13.5)	0.005
FEV1 (L)	2.9 (0.3)	2.7 (0.6)	0.079
FEV1 (%)	104.9 (12.2)	91.4 (15.7)	0.016
FEV1/FVC (%)	83 (5.7)	83.2 (7.5)	0.932
VO _{2peak} (mL kg m ⁻¹)	24.2 (5.3)	16.7 (5.4)	0.001
Peak power (W)	127.9 (32.6)	95.2 (31.5)	0.008
Power at VT ₁ (W)	57.7 (18.2)	35.4 (18.6)	0.002

Table 1. Descriptive characteristics of the patients with SARS-CoV-2 and control group. Data are provided as mean and standard deviation (SD). BMI body mass index, CG control group, FEV1 forced expiratory volume in the first second, FVC forced vital capacity, SARS-CoV-2 severe acute respiratory syndrome coronavirus type 2, VO_{2peak} peak oxygen uptake, VT₁ first ventilatory threshold. Significant values are given in bold.

vidually adjusted¹⁸. To determine the VO_{2SC} (Phase III), the data of pulmonary VO₂ was registered with an average interval of 3 s. Finally, the VO_{2SC} was determined in each participant: $\Delta\text{VO}_{2\text{SC}} = \text{VO}_{2\text{peak}} - (\text{VO}_{2\text{B}} + \Delta\text{VO}_{2\text{FP}})$ ¹⁸.

Evaluation of mechanical efficiency. The ME during the constant-load test was estimated as follows. The corresponding energy expenditure (EE) was calculated. The net VO₂ was obtained by subtracting resting VO₂ from the total VO₂ throughout the exercise. The net EE was calculated as: $(4.94 \times \text{RER} + 16.04) \times (\text{VO}_{2\text{net}}, \text{in ml min}^{-1}) \times 60^{-1}$ ¹⁹. The ME was also calculated in net terms: work converted in watts \times net EE $\times 100^{-1}$ ²⁰.

Evaluation of ventilatory efficiency. In the incremental and constant CPX ventilatory efficiency was determined as the slope of the relationship between VE and VCO₂ (VE·VCO₂⁻¹ slope)^{4,21}. In the incremental CPX, the VE·VCO₂⁻¹ slope was calculated from the beginning of the incremental exercise until the time of ventilatory compensation by linear regression^{22,23}.

Statistical analysis. The Shapiro–Wilk test was used to verify normal distribution of the data expressed as mean and the standard deviation (SD) and the mean and the corresponding 95% confidence intervals (95%CI). Analysis of variance was performed to determine differences between the two study groups in the normal variables and the Mann–Whitney U test was used for non-normal variables.

To determine the magnitude of the difference in the variables analyzed, the *d* of Cohen was used to test the effect size, which was defined as large with $d \geq 0.80$, moderate with $d \geq 0.40$ and small with $d < 0.40$ ²⁴. A Pearson correlation coefficient was applied to determine significant relations among the variables analyzed. Statistical significance was set as $p < 0.05$. The SPSS software package version 25.0 for Mac (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses.

Ethics statements. The study was approved by the Committee of Ethics and Investigation of the Mataró hospital (Code: 89/20). The study protocol was performed according to the principles of the Declaration of Helsinki, Good Practice Guidelines and local applicable regulations.

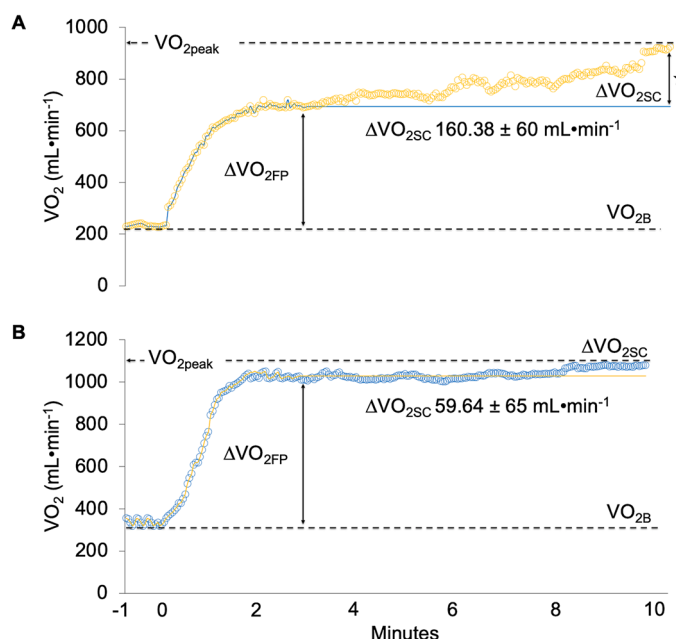
Consent to participate. All participants signed for written informed consent.

Results

Table 1 shows the main characteristics of the two study groups at baseline, the spirometry and incremental CPX results. The most relevant characteristics of the patients with SARS-CoV-2 are shown in Table 2.

Slow component of VO₂. There was a significant increase in the VO_{2SC} in the patients with SARS-CoV-2 in comparison with the healthy participants ($F = 20.24$, $P < 0.001$, $d = 1.53$) (Figs. 1 and 2A).

Hospital admission, yes (%)	8 (47.1%)
ICU admission, yes (%)	5 (29.4%)
ICU admission days	14.3 (7.3)
Days of hospital admission	25.4 (13.8)
Days of mechanical ventilation	8.5 (0.7)
Tracheostomy (no, %)	8 (100%)
Prone positioning (yes, %)	14 (53.8%)
Apache II/ICU admission	10.5 (4)

Table 2. Clinical characteristics of the patients with SARS-CoV-2. ICU intensive care unit.**Figure 1.** Kinetics of oxygen consumption (VO_2) during the constant load test at the intensity of the first ventilatory threshold (VT_1). **(A)** In patients with SARS-CoV-2. **(B)** Control group. The orange line (circles) corresponds to the data collected by the patients with SARS-CoV-2. The blue line (circles) corresponds to the data collected by the control group. The solid blue line corresponds to the assumed steady state of expected VO_2 at an intensity of VT_1 in the patients with SARS-CoV-2. The solid orange line corresponds to the assumed steady state of expected VO_2 at an intensity of VT_1 in control group. Data for VO_2 kinetics are provided as the mean of all participants. ★ Patients with SARS-CoV-2 significantly increased the slow component of VO_2 ($\text{VO}_{2\text{SC}}$) compared to the control group ($p < 0.001$). $\Delta\text{VO}_{2\text{FP}}$ increase in oxygen uptake in the fundamental phase, $\text{VO}_{2\text{B}}$ baseline oxygen consumption.

Mechanical and ventilatory efficiency. The ME significantly decreased in patients with SARS-CoV-2 with respect to the control group ($F = 4.24$, $P = 0.04$, $d = -1.10$) (Fig. 2B).

In relation to ventilatory efficiency, the $\text{VE} \cdot \text{VCO}_2^{-1}$ slope significantly increased in the patients with SARS-CoV-2 in comparison with the control group during the incremental test ($F = 16.60$, $P < 0.001$, $d = 1.67$) (Fig. 2C) and in the constant load test ($F = 19.23$, $P < 0.001$, $d = 2.21$) (Fig. 2D).

Highly significant correlations were observed between VE and VCO_2 during the incremental test ($r = 0.96$; $P < 0.001$) (Fig. 3A) and the constant load test ($r = 0.86$; $P < 0.001$) (Fig. 3B) in the SARS-CoV-2 patients. In addition, there was a significant inverse correlation between the ventilatory efficiency obtained in the incremental test and the ME achieved during the constant load in the patients with SARS-CoV-2 ($r = -0.73$; $P = 0.001$) (Fig. 3C). This correlation was not confirmed in the control group ($P > 0.05$) (Fig. 3D).

Discussion

To the best of our knowledge, this is the first study to assess the $\text{VO}_{2\text{SC}}$, ME and ventilatory efficiency in adult women recovered from SARS-CoV-2 during a constant-load test at VT_1 intensity. The most relevant finding of this study was that patients recovered from SARS-CoV-2 presented an elevated $\text{VO}_{2\text{SC}}$, deteriorated ME and significant ventilatory inefficiency in comparison with the control group of healthy women. Furthermore, the patients with COVID-19 with better ventilatory efficiency showed increased ME during the constant-load test.

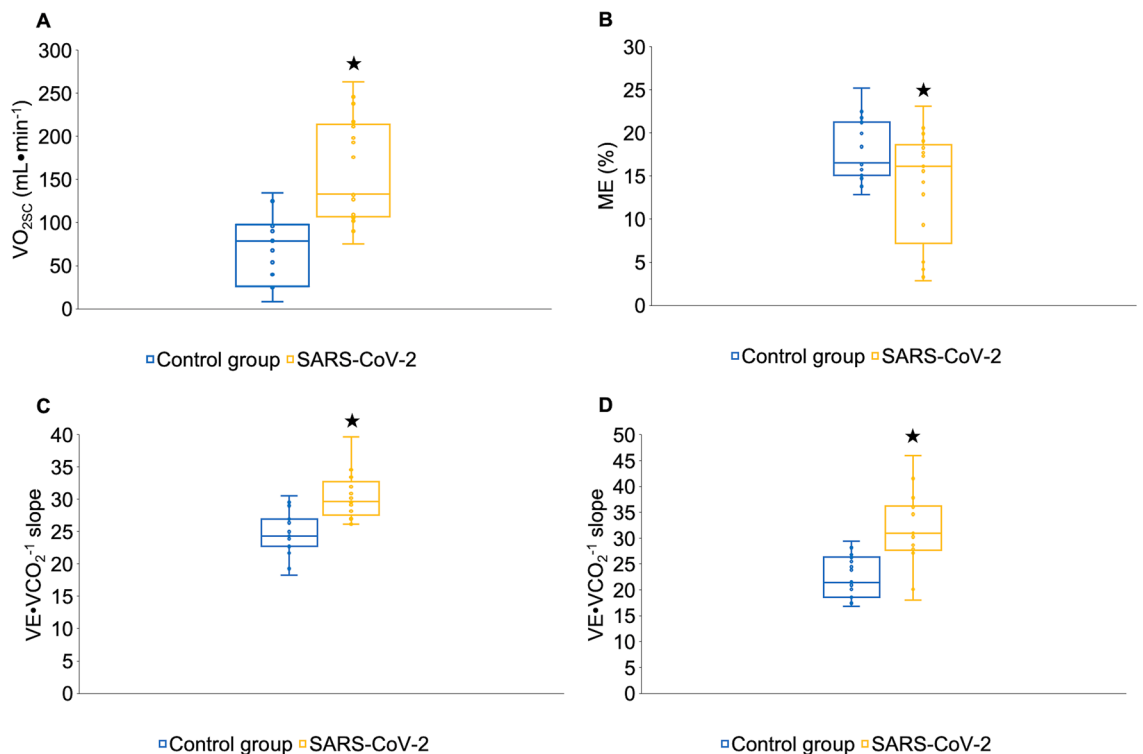


Figure 2. Differences between the patients with SARS-CoV-2 and the control group. **(A)** Slow component of VO_2 ($\text{VO}_{2\text{SC}}$) during the constant-load test at the intensity of the first ventilatory threshold (VT_1). **(B)** Mechanical efficiency (ME) during the constant-load test at the intensity of the VT_1 . **(C)** Ventilatory efficiency during incremental cardiopulmonary test. **(D)** Ventilatory efficiency during the constant-load test at the intensity of the VT_1 . Data are given as mean and error bars correspond to 95% confidence intervals (95% CI). ★ The patients with SARS-CoV-2 increased the $\text{VO}_{2\text{SC}}$ ($p < 0.01$) and the $\text{VE} \cdot \text{VCO}_2^{-1}$ slope ($p < 0.001$), and decreased the mechanical efficiency compared to the healthy control group ($p < 0.05$).

We can state that adult women recovered from SARS-CoV-2 suffered a greater impaired pulmonary and muscle function during moderate exercise than healthy adult women.

No previous study has assessed the $\text{VO}_{2\text{SC}}$, ME and ventilatory efficiency during a constant-load test in adult women recovered from COVID-19. Therefore, the discussion of the results was based on data reported by other studies in diseases with impaired pulmonary and muscle function during exercise.

We observed a substantial increase in the $\text{VO}_{2\text{SC}}$ in patients with COVID-19 compared to the control group. This elevation was especially notable if it is taken into account that the exercise performed at a constant-load at an intensity of the VT_1 should stimulate a stable state or plateau in VO_2 behavior⁴. While a stable state was observed in the VO_2 kinetics in healthy women, in the patients with COVID-19 there was a progressive increase in the $\text{VO}_{2\text{SC}}$, especially at the end of the test.

In comparison with our study, Chiappa et al. reported a higher $\text{VO}_{2\text{SC}}$ in both patients with chronic obstructive pulmonary disease (COPD) ($202 \pm 99 \text{ mL min}^{-1}$) and in the control group ($185 \pm 89 \text{ mL min}^{-1}$)⁵. Similar results were described by Laveneziana et al. in patients with COPD ($191 \pm 131 \text{ mL min}^{-1}$)²⁵. The differences observed with respect to our study could be attributed to the constant-load tests being more intense in both studies in terms of relative intensity (~75% of the peak load). The patients with COVID-19 and the healthy participants pedaled at a load intensity of ~37% and ~45%, respectively, of the peak power. The intensity of relative load (%) performed by the patients with SARS-CoV-2 was approximately half that reported in the above mentioned studies^{5,25}.

The physiological mechanisms producing the increase in $\text{VO}_{2\text{SC}}$ are uncertain, especially in cardiorespiratory diseases since the power or the equivalent load at the intensity of the lactate threshold or VT_1 means, in theory, the greater power or load the increase in the $\text{VO}_{2\text{SC}}$ does not produce. Elevated $\text{VO}_{2\text{SC}}$ response only occurs at intensities above the lactate threshold and the VT_1 ^{4,26}. It seems that a mild-moderate intensity such as VT_1 conditions the behavior of the $\text{VO}_{2\text{SC}}$ in patients recovered from COVID-19 to a greater extent than in other diseases with cardiorespiratory involvement at a similar or even lower relative intensity^{8,27}. Studies evaluating the kinetics of VO_2 at lower and higher intensities are needed to corroborate these suppositions in patients recovered from COVID-19.

As mentioned previously, the trend of the VO_2 kinetics observed in patients recovered from COVID-19 demonstrated a significant increase, especially at the end of the test. It can be assumed that this increase in $\text{VO}_{2\text{SC}}$ was associated with a progressive decline in muscular efficiency and²⁸, consequently, with the appearance of metabolic fatigue in response to the transition towards a more anaerobic metabolism^{28–30}. This muscular inefficiency induced by the $\text{VO}_{2\text{SC}}$ could be related to forced delayed recruitment of less efficient motor units (type II) from the oxidative point of view, simply to compensate the production of attenuated strength in motor units

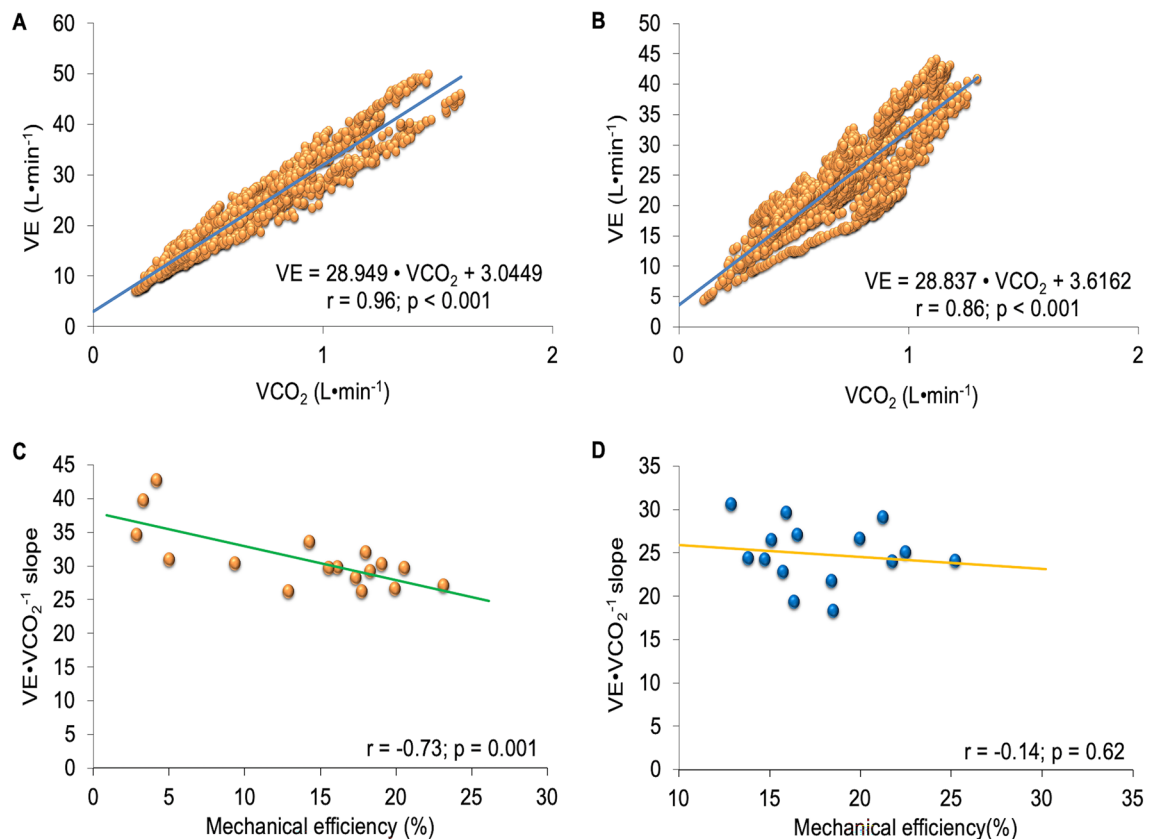


Figure 3. Correlations between variables: (A) $VE \cdot VCO_2^{-1}$ slope during incremental cardiopulmonary test in patients with SARS-CoV-2. (B) $VE \cdot VCO_2^{-1}$ slope during the constant load test at the intensity of the first ventilatory threshold (VT_1) in patients with SARS-CoV-2. (C) Mechanical efficiency during the test at constant load at VT_1 and the $VE \cdot VCO_2^{-1}$ slope during the incremental test in patients with SARS-CoV-2. (D) Mechanical efficiency during the test at constant load at VT_1 and the $VE \cdot VCO_2^{-1}$ slope during the incremental test in the control group.

already active during pedaling. In this physiological and metabolic context, preferential glycogen depletion of type I muscle fibers would be produced³¹. The recruitment of type II motor units has been suggested as a more acceptable explanation to understand the increase of the VO_{2SC} ^{6,7}. It is likely that 10 min of exercise at a VT_1 intensity stimulated premature and progressive recruitment of less efficient motor units in the patients recovered from SARS-CoV-2.

The ME could, at least in part, explain the behavior of the VO_{2SC} estimating the losses of muscular efficiency⁶. The results of ME observed in the constant-load test in female patients recovered from COVID-19 (~14% of ME at 37% of peak power) were lower than those achieved by the control group (~18% at 45% of peak power), and those reported by Baarends et al. who described net mean values of 15.5% in patients with COPD at an intensity corresponding to 50% of the peak load during a constant-load test³². Similar values of 16% were reported in patients with mild and moderate COPD at an intensity of 50% of the maximum power during a constant-load test³³. In any case, this demonstrates that values less than 17% in patients with COPD are indicative of reduced ME³².

We previously demonstrated that patients with COVID-19 showed a decreased delta efficiency similar to that observed in patients with COPD and ischemic heart disease during an incremental test³⁴. Other studies with patients recovered from the acute phase of COVID-19 have shown that patients with decreased exercise capacity showed a higher degree of deconditioning and lower levels of performance and earlier termination, with a lower work during a CPX³⁵. Probably, lower ME and deconditioning observed in patients recovered from COVID-19 could be related with an impaired O_2 extraction and use caused by a direct effect of viral load on muscle tissue³⁶. It seems that the reduction in ME could be related to the energy expenditure in the skeletal muscle. Layec et al. proposed a greater ATP cost during muscle contraction as the main cause of more reduced ME in patients with COPD³⁷. This increase in energy expenditure is generally associated with an increase in the proportion of type II muscular fibers during exercise in patients with COPD³⁸. The higher forced recruitment of type II fibers could justify, at least in part, an impaired extraction and use of O_2 , decreasing ME in female patients recovered of COVID-19 during a constant-load exercise of light-moderate intensity.

Other studies have proposed unusually low levels of fatty acid β -oxidation and altered lactate production by skeletal muscle as a functional limitation in patients with post-acute sequelae of SARS-CoV-2 infection³⁹. In theory, a high blood lactate concentration at lower exercise intensities suggests mitochondrial dysfunction⁴⁰.

Mitochondrial dysfunction has been evidenced as an inherent cause in understanding the pathogenesis of post-acute sequelae of SARS-CoV-2 infection in patients with preserved pulmonary and cardiac function³⁹.

Patients with a severely deteriorated ME are characterized by increased ventilatory response to exercise and by a reduction of the maximum capacity to perform exercise³². Consequently, the efficiency of pulmonary gas exchange is reduced, producing unadjustment between VE/perfusion, thereby increasing ventilatory inefficiency⁴. In patients recovered from SARS-CoV-2, the $VE \cdot VCO_2^{-1}$ slope increased demonstrating reduced ventilatory efficiency in comparison with the control group. This pulmonary dysfunction could affect perfusion in active muscle reducing tolerance to exercise⁴¹. The patients presenting the most reduced ME showed greater ventilatory inefficiency, likely negatively affecting the VE and perfusion in the lungs and muscles, thus decreasing exercise capacity⁴¹. This was not corroborated in the healthy women at an intensity of the VT_1 .

Rinaldo et al. did not find significant differences between patients with preserved and those with decreased exercise capacity in ventilatory efficiency³⁵. The authors concluded that COVID-19 survivors showed a mild reduction in their exercise capacity without relevant functional sequelae in the ventilatory and gas exchange response to exercise after 3 months. The reduction in exercise capacity was probably caused by muscle deconditioning. Unlike our study, these authors did not analyze ME. We likely found that patients with decreased ME showed lower ventilatory efficiency due to the timing of the tests (6–8 weeks after the patients recovered from COVID-19). Three months could be enough time to recover ventilatory efficiency in COVID-19 survivors with decreased exercise capacity³⁵ or impaired ME. Maybe, female patients with COVID-19 could recover pulmonary function before muscle function in the medium-long term. More studies are needed to confirm these hypotheses.

Although ventilatory efficiency was lower in patients recovered from COVID-19 compared to the group of healthy women, the values of the $VE \cdot VCO_2^{-1}$ slope could not be considered pathological in patients recovered from COVID-19³⁵. $VE \cdot VCO_2^{-1}$ slope values greater than 34 are used as a reference to determine important deterioration in several diseases¹³.

It was found that the ME and ventilatory efficiency during exercise declined in patients recovered from COVID-19, subsequently producing a hypothetical greater oxygen cost in the respiratory process probably directed, at least in part, by an increase in the VO_{2SC} ³². While it appears that adult females recovered from COVID-19 have increased VO_{2SC} and impaired ME and ventilatory efficiency, further studies are needed to establish a possible physiological causal relationship between the kinetics of VO_2 , ME and ventilatory efficiency in female patients recovered from SARS-CoV-2.

Finally, FVC (%) and FEV (%) were significantly lower in female patients recovered from COVID-19 than in healthy female group. Although spirometry values of FVC (%) and FEV (%) were not considered pathological in female patients recovered from COVID-19, they could be related to complications of COVID-19 pneumonia. In addition, BMI in the COVID-19 group (overweight) was also significantly higher than in the control group (normal weight). This could also condition the results during CPX in relation to ME, ventilatory efficiency and the VO_{2SC} .

Several limitations should be considered. The sample size was small. The group of women recovered from COVID-19 was a heterogeneous group consisting of patients who were hospitalized, patients admitted to the intensive care unit, and patients who were not hospitalized. The degree of severity of the SARS-CoV-2 disease (hospitalized vs. non-hospitalized) could have influenced the interpretation of the results. More studies analyzing the impact of hospitalization, intensive care unit and non-hospitalization on the VO_{2SC} , ME and ventilatory efficiency in COVID-19 survivors will be needed to substantiate such claims.

Conclusions

Female patients recovered from SARS-CoV-2 had significant pulmonary and muscle dysfunction compared with healthy women of similar characteristics. These findings were corroborated by detecting an increase in the VO_{2SC} and a deteriorated ME and ventilatory efficiency during the constant-load test.

Strength and endurance rehabilitation programs should be considered during the early phase of recovery in patients recovered from SARS-CoV-2.

Data availability

All data of this study are available from the corresponding author on reasonable request.

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References

- Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *Lancet* **395**, 497–506 (2020).
- Li, Y. C., Bai, W. Z. & Hashikawa, T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol.* **92**, 552–555 (2020).
- Townsend, L. *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS ONE* **15**, e0240784 (2020).
- Balady, G. J. *et al.* American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. *Circulation*. **122**, 191–225 (2010).
- Chiappa, G. R. *et al.* Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: Relationship to central cardiovascular dynamics. *J. Appl. Physiol.* **104**, 1341–1350 (2008).
- Gaesser, G. A. & Poole, D. C. The slow component of oxygen uptake kinetics in humans. *Exerc. Sport Sci. Rev.* **24**, 35–71 (1996).
- Whipp, B. J. The slow component of O₂ uptake kinetics during heavy exercise. *Med. Sci. Sports Exerc.* **26**, 1319–1326 (1994).

8. Reuveny, R. *et al.* High-intensity interval training accelerates oxygen uptake kinetics and improves exercise tolerance for individuals with cystic fibrosis. *BMC. Sports Sci. Med. Rehabil.* **12**, 1–13 (2020).
9. Jabbour, G. & Iancu, H. D. Mechanical efficiency improvement in relation to metabolic changes in sedentary obese adults. *BMJ. Open Sport Exerc. Med.* **1**, e000044 (2015).
10. Keir, D. A. *et al.* The slow component of pulmonary O₂ uptake accompanies peripheral muscle fatigue during high-intensity exercise. *J. Appl. Physiol.* **121**, 493–502 (2016).
11. Dimopoulos, K. *et al.* Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* **113**, 2796–2802 (2006).
12. Goulart, C. D. L. *et al.* The value of cardiopulmonary exercise testing in determining severity in patients with both systolic heart failure and COPD. *Sci. Rep.* **10**, 4309 (2020).
13. Arena, R., Myers, J. & Guazzi, M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail. Rev.* **13**, 245–269 (2008).
14. Arias-López, C. *et al.* Validación del poder predictivo de los Grupos de Morbilidad Ajustada (GMA) respecto de otras herramientas de estratificación de la población. *Rev. Esp. Salud Pública.* **94**, e202007079 (2020).
15. Knaus, W. A., Draper, E. A., Wagner, D. P. & Zimmerman, J. E. APACHE II: A severity of disease classification system. *Crit. Care Med.* **13**, 818–829 (1985).
16. Skinner, J. S. & McLellan, T. M. The transition from aerobic to anaerobic metabolism. *Res. Q. Exerc. Sport.* **51**, 234–248 (1980).
17. Keir, D. A. *et al.* Influence of muscle metabolic heterogeneity in determining the Vo_{2p} kinetic response to ramp-incremental exercise. *J. Appl. Physiol.* **120**, 503–513 (2016).
18. Murgatroyd, S. R., Ferguson, C., Ward, S. A., Whipp, B. J. & Rossiter, H. B. Pulmonary O₂ uptake kinetics as a determinant of high-intensity exercise tolerance in humans. *J. Appl. Physiol.* **110**, 1598–1606 (2011).
19. Garby, L. & Astrup, A. The relationship between the respiratory quotient and the energy equivalent of oxygen during simultaneous glucose and lipid oxidation and lipogenesis. *Acta Physiol. Scand.* **129**, 443–444 (1987).
20. LaFortuna, C. L., Proietti, M., Agosti, F. & Sartorio, A. The energy cost of cycling in young obese women. *Eur. J. Appl. Physiol.* **97**, 16–25 (2006).
21. Hoshimoto-Iwamoto, M. *et al.* Determination of the VE/VCO₂ slope from a constant work-rate exercise test in cardiac patients. *J. Physiol. Sci.* **58**, 291–295 (2008).
22. Koike, A. *et al.* Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest* **121**, 1581–1588 (2002).
23. Wasserman, K., Hansen, J. E., Sue, D. Y., Stringer, W. W. & Whipp, B. J. Principles of Exercise Testing and Interpretation. Philadelphia: Lippincott Williams & Wilkins; 33–4 (2005).
24. Cohen, J. A power primer. *Psychol. Bull.* **112**, 155–159 (1992).
25. Laveneziana, P., Palange, P., Ora, J., Martolini, D. & O'Donnell, D. E. Bronchodilator effect on ventilatory, pulmonary gas exchange, and heart rate kinetics during high-intensity exercise in COPD. *Eur. J. Appl. Physiol.* **107**, 633–643 (2009).
26. Jones, A. M. & Burnley, M. Oxygen uptake kinetics: An underappreciated determinant of exercise performance. *Int. J. Sports Physiol. Perform.* **4**, 524–532 (2009).
27. Zhang, Y. Y. *et al.* O₂ uptake kinetics in response to exercise. A measure of tissue anaerobiosis in heart failure. *Chest* **103**, 735–741 (1993).
28. Garnacho-Castaño, M. V. *et al.* Oxygen uptake slow component and the efficiency of resistance exercises. *J. Strength Cond. Res.* **35**, 1014–1022 (2021).
29. O'Connell, J. M., Weir, J. M. & MacIntosh, B. R. Blood lactate accumulation decreases during the slow component of VO₂ without a decrease in muscular efficiency. *Pflugers Arch.* **469**, 1257–1265 (2017).
30. Garnacho-Castaño, M. V. *et al.* The slow component of oxygen uptake and efficiency in resistance exercises: A comparison with endurance exercises. *Front. Physiol.* **10**, 1–14 (2019).
31. Vøllestad, N. K. & Blom, P. C. Effect of varying exercise intensity on glycogen depletion in human muscle fibres. *Acta Physiol. Scand.* **125**, 395–405 (1985).
32. Baarends, E. M., Schols, A. M., Akkermans, M. A. & Wouters, E. F. Decreased mechanical efficiency in clinically stable patients with COPD. *Thorax* **52**, 981–986 (1997).
33. Beijers, R. J. H. C. G. *et al.* The effect of acute and 7-days dietary nitrate on mechanical efficiency, exercise performance and cardiac biomarkers in patients with COPD. *Clin. Nutr.* **37**, 1852–1861 (2018).
34. Pleguezuelos, E. *et al.* Severe loss of mechanical efficiency in COVID-19 patients. *J. Cachexia Sarcopenia Muscle.* **12**, 1056–1063 (2021).
35. Rinaldo, R. F. *et al.* Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur. Respir. J.* **58**, 2100870 (2021).
36. Kucuk, A., Cumhuri Cure, M. & Cure, E. Can COVID-19 cause myalgia with a completely different mechanism? A hypothesis. *Clin. Rheumatol.* **39**, 2103–2104 (2020).
37. Layec, G., Haseler, L. J., Hoff, J. & Richardson, R. S. Evidence that a higher ATP cost of muscular contraction contributes to the lower mechanical efficiency associated with COPD: preliminary findings. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **300**, R1142–R1147 (2011).
38. Whittom, F. *et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med. Sci. Sports Exerc.* **30**, 1467–1474 (1998).
39. de Boer, E. *et al.* Decreased fatty acid oxidation and altered lactate production during exercise in patients with post-acute COVID-19 syndrome. *Am. J. Respir. Crit. Care Med.* **205**, 126–129 (2022).
40. Parikh, S. *et al.* Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genet. Med.* **17**, 689–701 (2015).
41. Romer, L. M. & Polkey, M. I. Exercise-induced respiratory muscle fatigue: Implications for performance. *J. Appl. Physiol.* **104**, 879–888 (2008).

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Author contributions

Conception or design: E.P. and M.V.G.-C.; acquisition, analysis, or interpretation of data: All authors; drafting or revising; E.P., M.M. and M.V.G.-C.; final approval of the version: all authors. Agreement to be accountable for all aspects: all authors.

Competing interests

The authors declare no competing interests.

Additional information

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