Impact of COVID-19 on exercise pathophysiology. A combined cardiopulmonary and echocardiographic exercise study.

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ABSTRACT

Background. Survivors from COVID-19 pneumonia can present with persisting multisystem involvement (lung, pulmonary vessels, heart, muscle, red blood cells) that may negatively affect exercise capacity.

Methods. We sought to determine the extent and the determinants of exercise limitation in COVID-19 patients at the time of hospital discharge.

Results. Eighteen consecutive patients with COVID-19 and 1:1 age-, sex-, and body mass index-matched controls underwent: spirometry, echocardiography, cardiopulmonary exercise test and exercise echocardiography for the study of pulmonary circulation. Arterial blood was sampled at rest and during exercise in COVID-19 patients. COVID-19 patients lie roughly on the same oxygen consumption isophlets than controls both at rest and during submaximal exercise, thanks to supernormal cardiac output ($p<0.05$). Oxygen consumption at peak exercise was reduced by 30% in COVID-19 ($p<0.001$), due to a peripheral extraction limit. Additionally, within COVID-19 patients, hemoglobin content was associated with peak oxygen consumption ($R^2=0.46$, $p=0.002$)Respiratory reserve was not exhausted (median [IRQ], 0.59 [0.15]) in spite of moderate reduction of forced vital capacity (79±40%)Pulmonary artery pressure increase during exercise was not different between patients and controls. Ventilatory equivalents for carbon dioxide were higher in COVID-19 patients than in controls (39.5 [8.5] vs 29.5 [8.8], $p<0.001$), and such an increase was mainly explained by increased chemosensitivity.

Conclusions. When recovering from COVID-19, patients present with reduced exercise capacity and augmented exercise hyperventilation. Peripheral factors, including anemia and reduced oxygen extraction by peripheral muscles were the major determinants of deranged exercise physiology. Pulmonary vascular function seemed unaffected, despite restrictive lung changes.

New and noteworthy

- At the time of hospital discharge, COVID-19 patients present with reduced functional capacity and exercise hyperventilation.

- Peripheral factors, namely reduced oxygen extraction (myopathy) and anemia, which are not fully compensated by a supernormal cardiac output response, account for exercise limitation before exhaustion of the respiratory reserve.

- Enhanced chemoreflex sensitivity, rather increased dead space, mainly account for exercise hyperventilation.

- The pulmonary vascular response to exercise circulation of survived COVID-19 patients do not present major pathological changes

Keywords: COVID-19; cardiopulmonary exercise test; exercise echocardiography; hemodynamics

BACKGROUND

Novel coronavirus-19 disease (COVID-19) pandemic has affected more than 100 millions of people all around the world up to February 2nd [1]. Despite obvious concerns on mortality rates, 98% of subjects survived [1], but survival was often associated with residual fibrotic lung abnormalities at discharge from hospitalization, as witnessed by preliminary studies with chest CT-scans [2] and pulmonary function tests [3]. Given the often severe involvement of multiple organs body functions during COVID-19, other abnormalities might persist at the resolution of the acute phase, potentially affecting subjects' wellbeing. Various forms of pulmonary vascular involvement (pulmonary macro- or micro-embolism [4], as well as inflammatory endothelitis with neo-angiogenesis [5] and blunted hypoxic pulmonary vascoconstriction [6]) have been reported, especially in the most severe cases. Cardiac involvement has been described in a small but not negligible proportion of patients during the acute phase [7]. Additionally, the huge systemic inflammatory response during COVID-19 could lead to anemia, which is a common finding in these patients and reduces blood oxygen carrying capacity [8]. Furthermore, hospitalization for COVID-19 generally lasts for several weeks, is characterized by prolonged bed rest and administration of myotoxic medications, that can promote profound deconditioning and muscle atrophy, especially in patients admitted to the intensive care unit. Additionally, concern has been raised on the potential of COVID-19 to be directly or indirectly associated with myopathic changes [9,10]. However, the impact of all these multisystem alterations on patients' functional capacity at the time of hospital discharge after COVID-19 is still unknown. Based on the above considerations, we hypothesized that the oxygen flow from the mouth to mithocondria could be impaired at several steps (ventilatory or cardiac pump, pulmonary circulation, blood oxygen carrying capacity, muscular oxygen extraction) immediately after clinical resolution of COVID-19 pneumonia. Thus, we sought to quantify and describe the extent and the main mechanisms of exercise limitation in

these patients at the time of hospital discharge, combining cardiopulmonary exercise test with exercise echocardiography and comparing patients healed from COVID-19 with matched controls. Based on analogy with previous reports on survivors from Severe Acute Respiratory Syndrome, we anticipated that COVID-19 could be associated with a ~20% reduction of exercise capacity [11-13].

METHODS

COVID-19 patients

Between 22nd of April and 5th of May 2020, we consecutively assessed patients just before their hospital discharge from San Luca Hospital, Istituto Auxologico Italiano, Milan, where they have been admitted for PCR-positive COVID-19 pneumonia.

We included patients that, at the time of evaluation, were become PCR-negative, were judged clinically healed and weaned from oxygen, could perform an exercise test and did not present relevant pre-existing cardiac, respiratory or musculoskeletal comorbidities. In particular, we excluded patients with pre-existing reduced left ventricular (LV) ejection fraction (< 50%) or valvular heart disease, pulmonary embolism, chronic obstructive lung disease (COPD) GOLD class>II, muscular myopathy, active malignancy or cognitive decline.

On the day before hospital discharge, enrolled patients underwent a full cardiorespiratory assessment, including pulmonary function test, echocardiography at rest, cardiopulmonary exercise test combined with exercise echocardiography. In all patients, a radial artery catheter was inserted into the right radial artery, using sterile techniques and local anesthetic.

Control subjects

We queried the database of patients who underwent a full cardiorespiratory assessment for unexplained dyspnea at Istituto Auxologico Italiano, Milan, between September 2016 and May 2018. This cardiorespiratory assessment consisted of lung spirometry, cardiopulmonary exercise test combined with exercise stress echocardiography and dynamic assessment of operating lung volumes. We excluded patients with a cardiac or respiratory limitation to exercise [14], patients with reduced LV ejection fraction (< 50%) or valvular heart disease, those with echocardiographic estimate of high LV filling pressure, pulmonary embolism, COPD GOLD > grade II, muscular myopathy, active malignancy or cognitive decline.

Control subjects were matched 1:1 with COVID-19 patients for age, sex and body mass index (BMI). In case that more than one control subject matched with a COVID-19 patient, we chose the subject who underwent exercise cardiorespiratory study more recently.

The Ethics Committees of the Istituto Auxologico Italiano approved the study on 21st of April 2020 (procotol number 2020_04_21_04). All COVID-19 patients signed a written informed consent at the time of enrollment before undergoing a full cardiorespiratory assessment. All controls had signed a written informed consent for the use of their data for research purposes.

Pulmonary function tests

Lung spirometry was performed using automated equipment (Vmax SensorMedics 2200, Yorba Linda, CA, USA).

Echocardiography at rest and during exercise

Echocardiography at rest was performed according to current recommendations of the European/American Society of Echocardiography [15,16]. Left and right ventricular strain analysis was possible in COVID-19 patients only.

Exercise stress echocardiography was performed at the same time of cardiopulmonary exercise test (see below). At rest, during the last minute of the warm-up phase and at peak exercise, consecutive pairs of tricuspid regurgitant jet velocity and velocity time integral of the left ventricular outflow tract were collected. These 2 parameters allow the estimation of pulmonary artery pressure (PAP) and cardiac output (CO) respectively, as previously described [17-19]. We have already demonstrated the accuracy of exercise echocardiography for the assessment of pulmonary hemodynamics in our laboratory [18]. Results reflect the agreement of 2 independent and experienced cardiologists. Multipoint PAP-CO slopes were calculated from linear regressions. Average slopes were also calculated from pooled mPAP-CO relationships of each study group using an adjustment for individual variability as previously described [19]. At the same time, also tissue Doppler imaging of the tricuspid annulus was recorded, to assess S' wave, as a measure of right ventricular longitudinal systolic function. The ratio between S' wave and systolic PAP was computed as an estimate of right ventricular to pulmonary artery coupling, albeit it has been less validated than other echocardiographic parameters [20]. A single operator performed all echocardiographic examinations with a GE Logiq E9 ultrasound machine (General Electric Company, Boston, MA). Stored images were blindly reviewed and analyzed by two readers.

Cardiopulmonary exercise test

Patients wore a non-rebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200, Yorba Linda, CA, USA).

A symptom-limited exercise test was performed on a semi-recumbent cycle ergometer. Exercise started with a 20-30 W warm-up phase (depending on subject's fitness) lasting 3 minutes, followed by a personalized ramp increment in workload, in order to achieve exhaustion in 6-12 minutes [14]. Subjects were encouraged to exercise up to their maximal volitional effort, with the

aim of obtaining a peak respiratory quotient > 1.1. Key measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters, and dynamic operating lung volumes calculated from inspiratory capacity maneuvers. At rest, during the last minute of the warm-up phase and at peak exercise, a flow-volume loop maneuver was performed [21] roughly at the same time of echocardiographic acquisition, and, only in COVID-19 patients, two milliliters of blood were sampled from the radial artery catheter. An average of the last 30-second period of exercise was taken as peak value for the variables of interest. The VE/VCO_2 slope was calculated over the linear component of VE vs VCO_2 [22] Results reflect the agreement of 2 independent and experienced operators.

Derived cardiorespiratory parameters

The content of oxygen in arterial blood (CaO_2) was calculated using the following formula: $CaO_2=1.39*SaO_2*Hb+0.0031*PaO_2$ [16], where SaO_2 is oxygen saturation in arterial blood, Hb is hemoglobin and PaO_2 is arterial oxygen partial pressure. In controls, the minor role of PaO_2 in determining CaO_2 was neglected, given that a radial artery catheter was not routinely placed.

By resolving Fick equation to obtain the arterial-venous oxygen difference from the direct measure of oxygen consumption (VO_2) and from the echocardiographic estimate of cardiac output, we derived the content of oxygen in venous blood [23].

Physiological dead space was calculated in COVID-19 patients by using VE, VCO2, as well as $PaCO_2$ directly measured from arterial blood [24,25].

Statistics

In the absence of previous data on exercise limitation after COVID-19 at the time in which the study was conducted, but considering reports of ~20% reduction of exercise capacity after Severe Acute Respiratory Syndrome [11-13], we tested the hypothesis that VO_2 at peak exercise would be

20% lower in COVID-19 patients as compared with controls. Considering a power of 80% and a significance level (alpha) of 0.05, and a standard deviation of 20%, we needed to include 18 COVID-19 patients and 18 controls.

All continuous variables were reported as median and interquartile range [IQ] for homogeneity of data representation. Categorical data were reported as absolute numbers and proportions. Distribution of variables in terms of proximity to the normal curve and the homogeneity of variances were detected by Shapiro-Wilk test and Bartlett test, respectively. Numerical variables were analyzed with t test or Wilcoxon rank sum, according to their distributions. Categorical variables were analyzed with Chi-squared test or Fisher exact test in case of small cell sizes. Correlation analysis was performed with the Pearson product-moment or with Kendall's tau, where appropriate. Multiple linear regressions were performed to assess factors associated with VO_2 and the ratio between minute ventilation (VE) and carbon dioxide (VCO2) at peak. The variable selection for each model was performed by a stepwise method using Akaike's information criterion (AIC). All regression analysis met the assumptions for linearity, homoscedasticity, multicollinearity, and normality of residuals. An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using R Core Team (2020), Vienna, Austria.

RESULTS

General and echocardiographic characteristics

Out of 25 patients evaluated at the time hospital discharge after resolution of laboratory-confirmed COVID-19 pneumonia between 22nd of April and 5th of May 2020, 20 satisfied inclusion criteria for the study and 18 accepted to participate. They underwent a full cardiorespiratory assessment at the time of hospital discharge. Eighteen age-, sex- and BMI- matched controls were

chosen among 115 outpatients who underwent cardiopulmonary exercise test combined with exercise-stress echocardiography, pulmonary function test and dynamic assessment of operating lung volumes.

As shown in **Table 1,** it was a middle-aged, overweight population with a high prevalence of male sex. The main general characteristics of COVID-19 patients did not differ from control group (**Table 1**), including the burden of mild comorbidities. Obesity was slightly but non-significantly more prevalent in controls, in spite of a non-different BMI between the two groups.

Patients with COVID-19 spent in median 30 [23-37] days in the hospital, where they had been treated with antiretroviral agents, steroids, antibiotics, hydroxychloroquine, and low-molecular weight heparin, in all cases at anticoagulant dosage as per local recommendations. Five patients (28%) underwent mechanical ventilation, 9 patients (50%) received non-invasive ventilation and 4 patients (22%) necessitated only oxygen support.

Blood tests were within normal limits, except for mild anemia: COVID-19 patients presented with lower hemoglobin values than controls (11.3 [2.3] vs 14.5 [2.0] g/dL, $p<0.001$).

Cardiorespiratory function at rest

Lung volumes of patients recovering from COVID-19 were smaller than controls (**Table 1**), with a relative reduction of both forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) of 22% and 26% in median, respectively ($p<0.05$). Forty-five percent of COVID-19 patients presented with at least moderate restrictive lung disease, while 67% of controls had normal lung function tests ($p<0.01$).

At the same basal ventilation of controls, respiratory dynamics of COVID-19 were characterized by higher respiratory rate (24.0 [6.0] vs 18.5 [9.3] / min, $p=0.021$) with high dead space ventilation (V_D/V_T 0.63 [0.05]), higher end-inspiratory lung volume (1.97 [1.25] vs 1.06 [1.00] L, $p=0.002$; **e-**

Table 1, https://sandbox.zenodo.org/record/733386), higher ventilatory equivalents for carbon dioxide (VE/VCO_2 61 [7] vs 42 [16], p=0.003) and lower end-tidal carbon dioxide pressure ($PetCO_2$ 29 [2] vs 32 [7], p=0.023). SaO2 was in the normal range albeit slightly lower in COVID-19 as compared with controls (p<0.01).

CaO_2 of COVID-19 patient was lower than controls (p<0.01), and associated with hemoglobin levels (tau 0.62, p<0.001). Arteriovenous oxygen difference was lower in COVID-19 (p<0.01) but peripheral oxygen extraction at rest was not different between COVID-19 and controls.

Standard echocardiography did not show any relevant abnormality in COVID-19 patients, except for a mildly dilated right ventricle (**Table 3**). Global longitudinal strain of the left ventricle and right ventricular free wall strain in COVID-19 patients were -18 [4] and -22 [8] %, respectively. Accordingly, one third of COVID-19 patients presented with an abnormal left or right ventricular strain, defined by cut-off values > -17 and -20%, respectively.

Both cardiac output and PAP were higher in COVID-19 than controls (p<0.05), leading to similar total pulmonary resistance (TPR) in the 2 groups. The ratio between right ventricular S' wave and systolic PAP was not different between the two groups.

Cardiorespiratory function during exercise

Cardiorespiratory function at peak exercise is shown in **Table 2**. All patients affirmed to have performed a maximal volitional effort up to their limit. At peak exercise, VO_2 was lower in COVID-19 patients than in controls (p<0.001). The same held true for peak workload (64 [40] vs 128 [89] W, p<0.001). Ninety-five percent of COVID-19 patients had a reduced exercise capacity, with a peak VO_2 less than 70% of predicted in 61% of cases (vs 17% of controls, p=0.006). Also the VO_2/work slope was lower in COVID-19 than in controls (p<0.001).

Oxygen delivery and extraction during exercise

Figure 1 show cardiac output behavior as a function of arteriovenous oxygen difference and of peripheral oxygen extraction: COVID-19 patients lie roughly on the same isophlets than controls at rest and during submaximal exercise, at higher cardiac output and lower arteriovenous oxygen difference and peripheral extraction. Accordingly, the relationship between VO_2 and cardiac output was rightward shifted in patients with COVID-19: at any VO_2, cardiac output was higher in COVID-19 patients than in controls (**Figure 2**). At peak exercise, CaO_2, arteriovenous difference and peripheral oxygen extraction were lower in COVID-19 than in the control group ($p<0.05$). Absolute cardiac output value was not different between groups at peak exercise, but it was supernormal in COVID-19 when expressed as percentage of predicted values ($p=0.004$). This occurred in spite of a mild chronotropic incompetence and a reduced systemic arterial pressure response in COVID-19 as compared with controls ($p<0.05$). Finally, when analyzing COVID-19 patients alone, VO_2 at peak was associated both with CaO2 (tau= 0.58, $p=0.012$) and with hemoglobin ($R2=0.46$, $p=0.01$; **e-Figure 1**, https://sandbox.zenodo.org/record/733386) https://doi.org/10.5281/zenodo.4549376.

Ventilation during exercise

Overall, respiratory reserve was not exhausted in COVID-19 patients and similar to that of controls (**Table 2**). Additionally, the occurrence of expiratory or inspiratory flow limitation, as well as of dynamic hyperinflation during exercise did not differ between COVID-19 patients and controls (**Table 2 and e-Table 1**, https://doi.org/10.5281/zenodo.4549376). Only two patients had a pattern consistent with respiratory limitation to exercise, presenting reduced lung volumes at rest and a respiratory reserve of 16%, but only one had mild oxygen desaturation at peak (from 98 to 93%).

Ventilation during exercise was lower in COVID-19 patients than in control subjects, with lower tidal volume and higher respiratory rate ($p<0.05$). Nevertheless, ventilatory equivalents for O_2 and

CO_2, $PetO_2$, and VE/VCO_2 slope were higher in COVID-19 patients than in controls, while $PetCO_2$ was lower ($p<0.05$). Accordingly, exercise hyperventilation as expressed by the VE/VCO_2 and $PetCO_2$ was higher in COVID-19 patients also during submaximal exercise ($p<0.001$), and was mainly linked with a low $PaCO_2$ set-point (**Figure 3**). As a notable exception, only the two patients presenting with respiratory limitation to exercise configured as outliers from this latter plot, and both of them had high V_D/V_T (0.63 and 0.64, respectively). Complete blood gas analysis at rest and at peak exercise in COVID-19 patients is shown in **Table 3**.

Pulmonary circulation during exercise

Three COVID-19 patients and 7 controls did not have a tricuspid regurgitant jet at peak exercise ($p=0.137$). Pressure-flow pairs of COVID-19 patients at rest and during submaximal exercise were upward and rightward shifted as compared with controls, but lay on the same regression slope (**Figure 4**), with non-different peak values (TPR of the whole population: 3.5 [1.7] WU). Individual pressure-flow pairs as well as averaged slopes for both patients' groups are shown in **e-Figure 2** and **e-Figure 3** (https://sandbox.zenodo.org/record/733386). In COVID-19 patients, SPAP and TPR at peak resulted unrelated to SaO_2, PaO_2 and CaO_2. Moreover, right ventricular function, even when normalized for right ventricular afterload, was similar in COVID-19 and controls.

Cardiorespiratory adaptation to exercise according to COVID-19 severity

We performed an exploratory analysis to highlight between-groups differences according to the type of ventilatory support undertaken during hospitalization (mechanical ventilation, non-invasive ventilation, oxygen mask), as shown in **e-Table 2** and **e-Table 3** (https://sandbox.zenodo.org/record/733386). As expected, both the length of hospitalization, as well as that of ventilatory support, decreased from mechanical ventilation to non-invasive ventilation to oxygen ($p<0.05$). Patients treated with mechanical ventilation tended to have lower

lung volumes as well as lower VO_2 at peak, in spite of a not-exhausted ventilatory reserve. Patients treated with non-invasive ventilation were older, had non-significantly higher E/E' and higher PAP at rest, as well as higher PAP at peak in spite of non-different TPR. There were no major differences between the three groups in blood tests, echocardiographic parameters at rest and at peak exercise, as well as in oxygen delivery and extraction.

DISCUSSION

With this paper, we provide the first description of the cardiorespiratory adaptation to exercise in the recovery phase from COVID-19 pneumonia, at the time of hospital discharge. In particular, our results show that: 1) recovering COVID-19 patients presented a significantly reduced exercise capacity; 2) impairment of functional capacity was mainly related to peripheral factors (anemia and oxygen extraction) rather than a respiratory or cardiac limitation; 3) in spite of parenchymal lung disruption, pulmonary vascular function was not impaired after COVID-19; 4) exercise hyperventilation after COVID-19 is frequent and principally due to enhanced chemoreflex sensitivity rather than increased V_D/V_T . This information could be relevant not only for a better understanding of COVID-19 consequences, but also to give clearer indications to survivors on how they should behave once discharged from the hospital, especially in previously healthy subjects, who would expect to resume their usual lifestyle. In particular, our findings might help reassuring survivors from COVID-19 about the benignity of residual symptoms in most cases.

VO_2 at peak at the time of hospital discharge was reduced by 30% in COVID-19 patients. The extent of such functional impairment was larger than previous reports in survivors from severe acute respiratory syndrome caused by coronavirus, investigated either by 6-minute walking test (two studies) or standard cardiopulmonary exercise test (one study) later on during follow-up, i.e.

312 3-12 months after hospital discharge [11-13]. Nonetheless, the extent of such limitation is similar
313 to a recent report describing cardiorespiratory fitness in COVID-19 patients, 2-3 months after
314 disease onset 19 [26]. Coherently with such previous reports [11,26], and extending those
315 evidences providing a deeper insight in exercise pathophysiology, the great majority of our
316 patients did not present respiratory limitation to exercise (normal respiratory reserve, absence of
317 relevant expiratory or inspiratory flow limitation, or dynamic hyperinflation) despite restrictive
318 pulmonary changes accounting for a reduction of 34% of lung volumes.

319 Instead, functional limitation seems to be mainly caused by reduced oxygen content secondary to
320 anemia as well as by impaired peripheral extraction after COVID-19. In particular, COVID-19
321 patients lie roughly on the same VO_2 and VO_2/CaO_2 isophlets of control subjects both at rest and
322 during low-workload exercise, in spite of lower arteriovenous difference and oxygen extraction,
323 thanks to higher cardiac output. However, at peak exercise the further increase of VO_2 in COVID-
324 19 appeared to be mainly driven by cardiac output increase, while reaching an apparent limit of
325 oxygen extraction. This finding might reflect myopathic changes occurring as a consequence of
326 medications administered during the hospital stay (e.g. steroids, which were used in all our
327 patients) as well as of the potential direct or indirect myopathic damage from COVID-19 [9,10],
328 rather than muscle disuse. Indeed, it has been previously shown that prolonged bed rest should
329 impair more stroke volume reserve rather than peripheral extraction in healthy subjects [27]. At
330 variance, cardiac output reserve was supernormal in our COVID-19 patients, despite prolonged
331 bed rest. We may try to explain this finding based on the peculiar hyperinflammatory setting of
332 COVID-19, which can be associated with a longstanding high-output hemodynamic state [6].
333 Interestingly, such supernormal cardiac output reserve occurred in spite of subtle
334 echocardiographic abnormalities (mild right ventricular dilation and abnormal myocardial
335 deformation indexes in one third of patients at rest, which is coherent with previous reports of

cardiac involvement after COVID-19 [7]) and of blunted heart rate and systemic blood pressure responses to exercise, potentially indicating a persisting autonomic imbalance after COVID-19 [28]. Based on this latter, we may also speculate that such autonomic derangement might be associated with suboptimal distribution of cardiac output to exercising muscles, thus contributing to low peripheral oxygen extraction.

Furthermore, the cytokine storm and systemic inflammatory response that characterize COVID-19 can be responsible for iron-restricted erythropoiesis with acute phase anemia [8], which could persist for a quite long time after resolution of pneumonia. Since each gram of hemoglobin can bind about 100 mL of oxygen [29], also anemia was obviously associated with reduced VO_2. Thus, in COVID-19 patients, that uniformly presented with a limit in oxygen extraction as compared with control subjects, lower hemoglobin values were associated with lower peak VO_2. The combination of these two peripheral factors (anemia and suboptimal extraction) was only partially compensated by a supernormal cardiac output, thus limiting exercise capacity well before exhaustion of the respiratory reserve. This result is encouraging since anemia and myopathic changes are expected to spontaneously recover during extended follow-up [12].

Additionally, it is interesting to note that, despite significant parenchymal disruption, pulmonary vascular function of COVID-19 was similar to that of control subjects. The pressure-flow relationship of the pulmonary circulation was upward and rightward shifted in COVID-19 patients as compared with controls, with a similar ratio between pulmonary artery pressure and cardiac output, which is consistent with invasive hemodynamic findings obtained in mechanically-ventilated COVID-19 patients [6]. Nonetheless, TPR resulted in both groups at the upper limit of normal at peak exercise. Indeed, both population were overall at increased risk for having heart failure with preserved ejection fraction, based on age, clinical history and comorbidities [30]. At variance from a recent report in severe COVID-19 evaluated in the acute phase of disease, where

right ventricular to pulmonary artery coupling was independently associated with survival, in our cohort S'/systolic PAP was not different between survived COVID-19 patients and controls, neither at rest nor during exercise [31].

Another peculiar aspect of COVID-19 exercise pathophysiology is hyperventilation. VE/VCO_2 was high at rest and during exercise, due to enhanced chemoreflex sensitivity. Indeed, only two patients with respiratory limitation to exercise presented with a high VE/VCO_2 due to high V_D/V_T, while in all other patients, the ventilatory response was leftward shifted probably due to reflex, peripheral factors [24,25].

Study limitations

Despite we enrolled a small sample of COVID-19 patients, our study was adequately powered to detect meaningful differences in exercise pathophysiology between COVID-19 and control subjects. While the small sample size of our study may limit generalizability of our results, it did not prevent us from conducting an in-depth pathophysiological exploration of a representative population healed from severe COVID-19 pneumonia, that was evaluated with cardiopulmonary exercise test combined with blood gas analysis and echocardiography at the time of their hospital discharge. Furthermore, the characteristics of our population are in line with those of larger studies [32], with a quite fair distribution of the kind of ventilatory support required during hospitalization. However, the small representation of each group of patients corresponding to a given ventilatory support, prevented us from finding meaningful between-groups differences, an aim that goes beyond the scope of the present work. Furthermore, despite heterogeneous ventilatory support, in median our patients had a severe lung restriction after COVID-19.

Controls were not asymptomatic matched individuals, but outpatients who underwent a full cardiorespiratory assessment to investigate the etiology of shortness of breath, including 17% of

patients with mild COPD (GOLD I or II). Additionally, given the unresolved issues related to the non-invasive diagnosis of heart failure with preserved ejection fraction, we cannot exclude that some of these subjects (as well as of COVID-19 patients) may have had an early phase of such disease [33,34], explaining TPR at the upper limits of normal. However, control subjects ended up even after this test without any sign of cardiac or respiratory limitation to exercise, and presented a burden of mild comorbidities comparable to that of our representative COVID-19 population. Since a radial artery catheter was routinely placed only in COVID-19 survivors but not in controls, we could not have a comparison of blood gas analysis between controls and COVID-19 patients. However, having excluded control subjects with severe respiratory disease, we believe that this does not importantly affect the interpretation of our results. Finally, we could not measure lung diffusion properties in our patients. Nonetheless, in survivors from Severe Acute Respiratory Syndrome, the functional disability has been suggested to be out of proportion to the degree of lung function impairment [13].

INTERPRETATION

Exercise limitation is a frequent finding at the time of hospital discharge after COVID-19 pneumonia. Reduced oxygen content and extraction, secondary to anemia and myopathic changes, rather than respiratory, pulmonary vascular or cardiac impairment, were the main contributors to reduced exercise capacity. Additionally, enhanced chemoreflex sensitivity triggers exercise hyperventilation after resolution of COVID-19 pneumonia. These findings might help reassuring survivors from COVID-19 on the benignity of residual symptoms in most cases.

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CB, SC, GP contributed to conception and design; CB and SC contributed to acquisition; CB, SC, AF contributed to analysis; CB, SC, GBP, MS, LPB, GP contributed to interpretation; CB and SC drafted the manuscript; AF, GBP, MS, LPB, GP critically revised the manuscript; all authors gave final approval. CB, SC, GP had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no conflict of interest to disclose

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FIGURE LEGENDS

Figure 1. Cardiac output as a function of arteriovenous oxygen difference (on the left) and of peripheral oxygen extraction (on the right) at rest and during exercise.

Data are represented as mean ± standard error of the mean.

Abbreviations: CaO_2=arterial oxygen content; $C(a\text{-}v)O_2$=arteriovenous oxygen difference; CO=cardiac output

549 **Figure 2. Oxygen consumption as a function of cardiac output.** This relationship was rightward

550 shifted in COVID-19 patients as compared with controls at rest and during submaximal exercise.

551 Data are represented as mean ± standard error of the mean.

552 Abbreviations: CO=cardiac output; VO_2=oxygen consumption.

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Figure 3. Exercise hyperventilation in COVID-19 patients and in controls.

Abbreviations: $PaCO_2$=arterial partial pressure for carbon dioxide; $PetCO_2$=end-tidal partial pressure for carbon dioxide; VCO_2=carbon dioxide production; V_D=dead space; V_E=minute ventilation; V_T=tidal volume.

Figure 4. Pressure-flow relationship of the pulmonary circulation in COVID-19 patients and controls.

The horizontal dotted line marks the value of 30 mmHg; the oblique dotted line corresponds to a slope of the pressure/flow relationship of 3 mmHg/L/min.

Data are represented as mean ± standard error of the mean.

Abbreviations: CO=cardiac output; mPAP=mean pulmonary artery pressure

TABLES

Table 1. General characteristics of study population

	Control patients N=18	COVID-19 patients N=18	p-value
Demographics and anthropometrics			
Age, years	65 (20)	66 (21)	0.911
Male sex, N (%)	13 (72)	13 (72)	1.000
BMI, kg/m^2	26 (5)	26 (4)	0.298
Comorbidities			
Arterial hypertension, N (%)	11 (61)	11 (61)	1.000
Diabetes mellitus, N (%)	1 (6)	2 (11)	0.547
Obesity, N (%)	5 (28)	1 (6)	0.074
Smoke, N (%)	3 (17)	3 (17)	1.000
COPD, N (%)	3 (17)	3 (17)	1.000
CAD, N (%)	0 (0)	1 (6)	0.347
Atrial fibrillation			1.000
Paroxismal, N (%)	1 (6)	1 (6)	
Permanent, N (%)	1 (6)	1 (6)	
Pulmonary function test			
FVC, L	4.02 (2.33)	2.66 (1.47)	0.002
FVC, % predicted	101 (10)	79 (47)	0.009
FEV_1, L/min	3.06 (1.47)	2.01 (1.13)	0.016
FEV_1, % predicted	105 (22)	79 (40)	0.059
FEV_1/FVC	0.78 (0.09)	0.83 (0.11)	0.045
Echocardiography at rest			
LV EDV, ml	106 (21)	109 (39)	0.735
LV EF	0.61 (0.07)	0.58 (0.08)	0.801
LV mass index, g/m^2	67 (16)	85 (21)	0.027
LA volume, ml	53 (20)	57 (26)	0.373
E/E' average	8 (3)	9 (5)	0.450
RV diameter, mm	35 (6)	40 (7)	0.029
S' RV, cm/s	11 (4)	14 (3)	0.155
Hemodynamics, oxygen delivery and extraction at rest			
SBP, mmHg	134 (30)	130 (20)	0.343
SPAP, mmHg	25 (10)	27 (11)	0.034
S' RV /SPAP, cm/s/mmHg	0.54 (0.23)	0.49 (0.11)	0.817
HR, bpm	75 (15)	82 (20)	0.760
CO, L/min	4.3 (0.9)	5.3 (1.5)	<0.001
SaO_2, %	99.5 (2.5)	98.0 (2.0)	0.007
CaO_2, mL/dL	19.6 (2.9)	17.1 (4.8)	<0.001
CvO_2, mL/dL	12.3 (3.1)	10.5 (5.4)	0.318
$C(a\text{-}v)O_2$ mL/dL	7.3 (2.3)	5.7 (2.5)	<0.001
$C(a\text{-}v)O_2$ / CaO_2	0.37 (0.10)	0.36 (0.17)	0.219

Abbreviations: BMI=body mass index, CAD=coronary artery disease, CaO_2= content of oxygen in arterial blood, $C(a\text{-}v)O_2$=arteriovenous oxygen difference, CO=cardiac output, COPD=chronic obstructive lung disease, COVID-19=novel coronavirus-19 disease, EDV=end-diastolic volume, EF=ejection fraction, FVC= forced vital capacity, FEV_1= forced expiratory volume in one second, HR=heart rate, LA=left atrium, LV=left ventricle, RV=right ventricle, SaO2= arterial oxygen saturation, SBP=systolic blood pressure, SPAP=systolic pulmonary artery pressure.

Table 2. Ventilatory and hemodynamic parameters of study population at peak exercise.

	Control patients N=18	COVID-19 patients N=18	p-value
Oxygen flow			
VO_2, ml/kg/min	22.8 (9.3)	14.8 (6.1)	<0.001
VO_2, % predicted	90 (19)	59 (32)	<0.001
VO_2/work slope	10.9 (1.9)	8.1 (1.2)	<0.001
O_2 pulse, mL/bpm	12.3 (3.6)	9.1 (2.0)	0.002
SaO_2, %	97.0 (2.8)	96.8 (4.5)	0.042
CaO_2, mL/dL	19.5 (2.5)	16.9 (5.0)	0.001
CvO_2, mL/dL	3.3 (6.2)	6.3 (3.1)	0.081
C(a-v)O_2, mL/dL	15.3 (5.6)	11.7 (2.5)	<0.001
C(a-v)O_2 / CaO_2	0.81 (0.31)	0.66 (0.19)	0.006
RQ	1.18 (0.15)	1.08 (0.28)	0.263
Ventilatory adaptation			
VE, L/min	54.5 (36.1)	41.9 (20.6)	0.038
VE/MVV	0.45 (0.19)	0.41 (0.15)	0.369
RR, /min	32.5 (9.3)	34.5 (12.0)	0.035
VE/VO_2	32 (10)	40 (10)	0.023
VE/VCO_2	30 (9)	40 (9)	<0.001
$PetO_2$, mmHg	112 (9)	117 (8)	0.037
$PetCO_2$, mmHg	39 (10)	34 (5)	0.001
Dynamic hyperinflation, N(%)	10 (56)	7 (39)	0.317
Expiratory flow limitation, N (%)	5 (29)	3 (17)	0.370
VE/VCO_2 slope	28 (8)	32 (7)	0.007
Cardiovascular adaptation			
HR, bpm	142 (36)	120 (30)	0.023
HR, % predicted	89 (13)	78 (17)	0.009
CO, L/min	10.3 (2.8)	10.6 (2.7)	0.872
CO, % of predicted	86 (20)	105 (28)	0.004
SBP, mmHg	195 (31)	165 (38)	0.020
SPAP, mmHg	54 (28)	52 (10)	0.835
TPR, WU	3.6 (2.1)	3.4 (1.7)	0.646
S' RV, m/s	16 (3)	19 (5)	0.560
S' RV /SPAP, m/s/mmHg	0.41 (0.26)	0.36 (0.18)	0.831

Abbreviations: CaO_2= content of oxygen in arterial blood, C(a-v)O_2=arteriovenous oxygen difference, CO=cardiac output, HR=heart rate, MVV=maximal voluntary ventilation, O_2=oxygen, $PetO_2$=end-tidal pressure for oxygen, $PetCO_2$= end-tidal pressure for carbon dioxide, RQ=respiratory quotient, RR=respiratory rate, RV=right ventricle, SaO_2= arterial oxygen saturation, SBP=systolic blood pressure, SPAP=systolic pulmonary artery pressure, TPR=total pulmonary vascular resistance, VE=minute ventilation, VCO_2=carbon dioxide production, VO_2= oxygen consumption.

Table 3. Blood gas-analysis in COVID-19 patients at rest and at peak exercise.

	REST	PEAK EXERCISE	p-value
PH	7.44 (0.02)	7.40 (0.05)	<0.001
PaO_2, mmHg	81 (14.5)	79 (25)	0.271
$PaCO_2$, mmHg	38 (5)	37 (5)	0.328
(ET-a)O_2, mmHg	32 (19)	39 (26)	0.106
(a-ET)CO_2, mmHg	9 (6)	4 (6)	<0.001
Lac, mmol/L	1.0 (0.4)	3.5 (2.8)	<0.001
V_D/V_T	0.63 (0.05)	0.38 (0.16)	<0.001

Abbreviations: (a-ET)CO_2= delta arterial/end-tidal partial pressure for carbon dioxide, (ET-a)O_2= delta end-tidal/arterial partial pressure for oxygen, Lac=lactate, $PaCO_2$=arterial partial pressure for carbon dioxide, PaO_2=arterial partial pressure for oxygen, V_D/V_T=dead space ventilation.