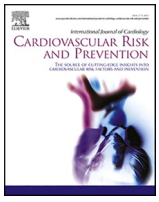
International Journal of Cardiology Cardiovascular Risk and Prevention 23 (2024) 200324

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Evaluation of myocardial work and exercise capacity in patients recovered from the severe form of COVID-19

Thiago Lins Fagundes de Sousa [a,b], Allan Robson Kluser Sales [a], Juliana Góes Martins Fagundes [a,b], Luis Fábio Barbosa Botelho [a,b], Francis Ribeiro de Souza [a], Guilherme Wesley Fonseca [c], André Luis Pereira de Albuquerque [a], Marcelo Dantas Tavares de Melo [b], Maria-Janieire de Nazaré Nunes Alves [a,*]

[a] Heart Institute (InCor), University of São Paulo Medical School, Brazil
[b] Medical Sciences Center of the Federal University of Paraíba, Brazil
[c] School of Physical Education and Sport, University of São Paulo, Brazil

ARTICLE INFO

Handling editor: D Levy

Keywords:
COVID-19
Myocardial work
Exercise
Heart rate recovery

ABSTRACT

Background: The impact of COVID-19 goes beyond its acute form and can lead to the persistence of symptoms and the emergence of systemic disorders, defined as long-term COVID.
Methods: We performed a cross-sectional study that included patients over 18 years of age who recovered from the severe form of COVID-19 at least 60 days after their discharge. Patients and controls were enrolled to undergo transthoracic echocardiography (TTE) using a more sensitive tool, myocardial work, in combination with cardiopulmonary exercise testing (CPET).
Results: A total of 52 patients and 31 controls were enrolled. Significant differences were observed in ejection fraction (LVEF; 62 ± 7 vs. 66 ± 6 %; p = 0.007), global longitudinal strain (LVGLS; −18.7 ± 2.6 vs. −20.4 ± 1.4 %; p = 0.001), myocardial wasted work (GWW; 152 ± 81 vs. 101 ± 54 mmHg; p = 0.003), and myocardial work efficiency (GWE; 93 ± 3 vs. 95 ± 2 %; p = 0.002). We found a significant difference in peak VO_2 (24.4 ± 5.4 vs. 33.4 ± 8.8 mL/kg/min; p < 0.001), heart rate (160 ± 14 vs. 176 ± 11 bpm; p < 0.001), ventilation (84.6 ± 22.6 vs. 104.9 ± 27.0 L/min; p < 0.001), OUES% (89 ± 16 vs. 102 ± 22 %; p = 0.002), T ½ (120.3 ± 32 vs. 97.6 ± 27 s; p = 0.002) and HRR at 2 min (−36 ± 11 vs. −43 ± 13 bpm; p = 0.010).
Conclusion: Our findings revealed an increased wasted work, with lower myocardial efficiency, significantly reduced aerobic exercise capacity, and abnormal heart rate response during recovery, which may be related to previously described late symptoms. The reduction in functional capacity during physical exercise is partly associated with a decrease in resting myocardial work efficiency. These findings strongly indicate the need to determine whether these manifestations persist in the long term and their impact on cardiovascular health and quality of life in COVID-19 survivors.

1. Introduction

Coronavirus disease (COVID-19) is associated with a high risk of death from a cardiovascular event, especially in the first weeks after infection, with the elderly and those with cardiovascular diseases being the most vulnerable [1]. Cardiovascular complications occur in approximately 18 % of hospitalized patients, resulting in a 45 % mortality rate compared to 13 % in those without such complications [2]. A study evaluating the Brazilian population (CoronaHeart) identified mechanical ventilation, a high level of C-reactive protein, and a high level of troponin as markers of in-hospital mortality [3].

Multiple mechanisms contribute to myocardial damage and the onset of numerous cardiovascular complications, including the rupture of inflammatory plaques, stent thrombosis, vascular dysfunction, stress related to the high cardiac output in septic patients, endotheliitis mediated by ACE receptor dysregulation, as well as hypoxemia resulting from severe pulmonary compromise and the potential toxic effects of treatment drugs [4–6]. The mechanism for persistent subclinical

* Corresponding author. Heart Institute (InCor), University of São Paulo Medical School, Av. Dr. Enéas de Carvalho Aguiar, 44 - Cerqueira Cesar - CEP: 05403-900 - São Paulo, Brazil.
E-mail address: janieire.alves@incor.usp.br (M.-J.N.N. Alves).

https://doi.org/10.1016/j.ijcrp.2024.200324
Received 8 May 2024; Received in revised form 8 August 2024; Accepted 15 August 2024
Available online 19 August 2024
2772-4875/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

dysfunction remains unknown; some magnetic resonance imaging studies suggest adverse remodeling, while another potential mechanism is endothelial and vascular dysfunction leading to subclinical impairment of left ventricular function persisting after the acute event [7,8].

Although many patients remain symptomatic, dyspnoea is present in half of patients after three months of recovery, and several post-COVID studies have shown that even among those with severe acute infection, systolic impairment measured by traditional echocardiographic analysis is rare, affecting only 9–11 % of patients [9]. Most of these studies evaluated ejection fraction, which, although a strong predictor of cardiovascular events, has low sensitivity in detecting subclinical events.

Myocardial strain assessment is a more sensitive marker for the early detection of changes in myocardial systolic function [10]. Among the strain indices, left ventricular global longitudinal strain (LVGLS) has emerged as a precise and reproducible measure. Another method that has gained prominence is the analysis of myocardial work (MW). This new measure is being studied as an evaluator of LV systolic function. It is less influenced than LVGLS by overload conditions, as it incorporates deformation and load in its analysis [11,12]. A recent study demonstrated that the pressure–strain curve measured by echocardiography can estimate LV performance in an analogous manner to invasive haemodynamics [13]. MW is highly reproducible and provides additional value to LVGLS in predicting adverse events. However, there are still no studies in the literature that have evaluated the behaviour of myocardial work in the post-COVID context and its relationship with aerobic capacity.

Equally important, cardiopulmonary exercise testing (CPET) has enabled the identification of the physiological mechanisms that affect patients' exercise capacity. Multiple studies have shown a decrease in peak oxygen consumption following an acute episode [14,15]. The primary mechanism of this seems to be muscle deficiency (oxygen extraction deficiency), which manifests mainly as submaximal exercise or early onset of the 1st ventilatory threshold. Although uncommon, central cardiocirculatory involvement has been described in some case series, and its mechanism is still poorly understood [16,17].

This study is the first to report the use of a new and refined approach in echocardiographic measurement in combination with CPET, with the aim of evaluating the behaviour of MW and its potential mechanisms in the aerobic performance of patients recovered from COVID-19.

Our main objective was to evaluate MW through the two-dimensional echocardiogram and the assessment of functional capacity through the CPET to assess the possible impact on the cardiovascular system and lower aerobic capacity of patients recovered from severe COVID-19. As secondary objectives, we aimed to correlate the results of MW measurements with the variables of the CPET, as well as correlate clinical, radiological, and laboratory data and length of hospitalization with the CPET and MW variables.

2. Methods

2.1. Study population

This was a single-centre, cross-sectional, observational study that included patients between 18 and 70 years of age who had recovered from severe COVID-19 (defined as intensive-care unit (ICU) admission with the need for oxygen supplementation by invasive or noninvasive mechanical ventilation). Patients with preexisting cardiac disease (heart failure, coronary artery disease, valvular heart disease, uncontrolled arrhythmias or those taking more than two antihypertensive medications), active cancer, renal failure requiring haemodialysis, cirrhosis, chronic obstructive pulmonary disease requiring oxygen therapy, diabetes requiring insulin, pregnancy, ultrasonographic limitations that prevented strain analysis or orthopaedic limitations or other contraindications to exercise testing were excluded from the study. A control group, matched for sex and age, was recruited for comparative purposes. This group consisted of individuals who did not meet any exclusion criteria and had not experienced symptomatic COVID-19.

Prior to inclusion, all participants provided written informed consent. The study received approval from the ethics and research committee of our centre under the number CAAE 45809421.7.0000.8069. Data from the electronic medical record of each hospitalization were collected. Pulmonary involvement data were derived from examination reports. The Total Severity Score (TSS) tool was employed to quantify and standardize the extent of pulmonary findings in chest tomography. At 60 days after hospital discharge, both the patients and control group underwent a transthoracic echocardiogram with measurement of MW and a cardiopulmonary exercise test performed during a single visit, according to established protocols [18–20].

2.2. Echocardiography

Two-dimensional transthoracic echocardiography was performed at the bedside using the Vivid S70 (GE Vingmed Ultrasound, Horten, Norway) with a 3Sc 1.3–4.0 MHz transducer, always by the same echocardiographer. The examination was performed with the patient in the left lateral decubitus position, and all images and measurements were acquired in accordance with the recommendations of the American Society of Echocardiography [19]. Video images corresponding to 3 cardiac cycles showing the QRS complex were acquired. All patients underwent non-invasive blood pressure measurement during the examination.

Myocardial deformation was assessed by two-dimensional dynamic images (3 cycles) in two, three and four chambers, with a frequency varying between 50 and 80 frames/second, acquired for the calculation of LVGLS. The opening and closing of the aortic and mitral valve were identified from the pulsatile Doppler of the aortic valve acquired in the apical three-chamber window. The endocardial and epicardial tracings were automatically tracked, and the acquisition was performed (after verification and adjustment by the examiner, when necessary). Using a 17-segment model, the software calculated GLS from the weighted average of the peak systolic longitudinal strain of each of the segments. Participants were excluded from the study if they had more than one segment with inadequate acquisition.

2.3. Myocardial work acquisition

MW and its variables were noninvasively calculated using two-dimensional echocardiography with the GE Vivid S70 machine. Participants' systolic blood pressure was measured by a sphygmomanometer immediately before the test (in the supine position), which was used as an estimate of LV systolic pressure. The software performed a noninvasive reconstruction of the LV pressure curve adjusted according to the durations of the ejection, isovolumetric contraction, and relaxation phases, defined from the times of opening and closing of the mitral and aortic valves. LV strain and pressure data were then synchronized with the times of valve events and systolic blood pressure, generating the following data for analysis:

Global work index (GWI): total work corresponding to the area of the pressure x strain curve, from mitral valve closure to mitral valve opening.

Global constructive work (GCW): total work that contributes to ventricular ejection: negative strain in systole + positive strain in isovolumetric relaxation time.

Global wasted work (GWW): work that does not contribute to LV ejection: strain positive in systole + strain negative in isovolumetric relaxation time.

Global work efficiency (GWE): fraction of constructive work from total work: GWE = (GCW)/(GCW + GWW) [21,22].

2.4. Cardiopulmonary exercise test

Stepwise incremental treadmill exercise was performed for the CPET

(Cortex Biophisik GmbH, Leipzig, Germany). A protocol that applied a linear increase in walking speed along with a curvilinear increase in treadmill inclination to produce a linear increase in work rate was used [23]. Before the exercise test, spirometry was performed for respiratory evaluation, according to the Brazilian guidelines for pulmonary function testing [24]. The following variables were evaluated: oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER = VO_2/VCO_2), end-expiratory pressure of carbon dioxide ($PETCO_2$), minute ventilation (Ve), tidal volume (Vt), dead space volume (Vd), respiratory rate (RR), heart rate (HR), oxygen pulse (VO_2/HR), load achieved, ventilatory equivalents (Ve/VCO_2 and Ve/VO_2), Ve/VCO2 slope, oxygen uptake efficiency slope (OUES), and the recovery time taken for VO2 to fall to 50 % of its peak value (T ½).

The reference values used for VO_2 and ventilatory thresholds were from Hansen and Wasserman and that for OUES% (OUES as a percentage of predicted) was from Hollenberg [25,26]. Exercise intolerance was defined as a peak VO_2 <85 % of the predicted value. Ventilatory limitation to exercise was defined when the breathing reserve was <15 %. The Wassermann flowchart was used to define circulatory limitation in participants when it led to a circulatory category, including ECG changes consistent with ischaemia or arrhythmia. Deconditioning was defined as a peak VO_2 <85 % of predicted with normal breathing reserve and no evidence of cardiocirculatory pathology (assessed by ECG, Ve/VCO_2 slope, and oxygen-pulse curve) [20].

2.5. Statistical analysis

Data are presented as the mean ± standard deviation or as median with lower and upper quartiles (95 % confidence interval) for continuous variables and as frequencies and percentages for categorical variables. To verify associations between categorical variables, the chi-square test was performed when applicable. In the case of numeric variables, we used Student's *t*-test or the Mann–Whitney test for parametric and nonparametric variables, respectively. Correlations between variables were assessed by Pearson's or Spearman's test. A p value lower than 0.05 was defined as statistically significant. Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). The sample size was not calculated, as no studies in the literature have performed the same comparative analysis.

3. Results

3.1. Baseline characteristics

Between January 10, 2021 and May 31, 2021, a total of 113 patients were admitted to our ICU for COVID-19 treatment. Of them, 68 were discharged from the hospital and were then enrolled in the study. Of these, 52 were able to complete the study protocol (Fig. 1). We also selected a group of 31 individuals as a control group, matched for age and sex.

The clinical characteristics of the study population are shown in Table 1. Participants with COVID-19 and the control group were similar in sex and age. Participants with COVID-19 had a higher body mass index than the control group. Regarding comorbidities, the most

Table 1
Clinical characteristics of study participants.

	COVID-19 n = 52	Control n = 31	p value
Age (years)	47 ± 8	46 ± 10	0.748
Male, n (%)	34 (65.4)	20 (64.5)	0.936
Height (cm)	170	170	0.844
Weight (kg)	84.3	76.3	0.017
Body mass index ($kg{\cdot}m^{-2}$)	29.2 ± 4.3	26.2 ± 3.4	0.002
Systolic blood pressure (mmHg)	141 ± 17	126 ± 10	<0.001
Diastolic blood pressure (mmHg)	83 ± 9	77 ± 6	0.001
Comorbidities, n (%)	15 (28)	6 (19)	0.436
Arrhythmias	4 (8)	0	0.292
Asthma	2 (4)	0	0.526
Diabetes	14 (27)	6 (19)	0.597
Hypertension			
Maximum pneumonia extent on	24 (46.2 %)		
chest CT	14 (26.9 %)		
−25–49 %	11 (21.2 %)		
−50–74 %	3 (5.8 %)		
- ≥75 %			
- no data			

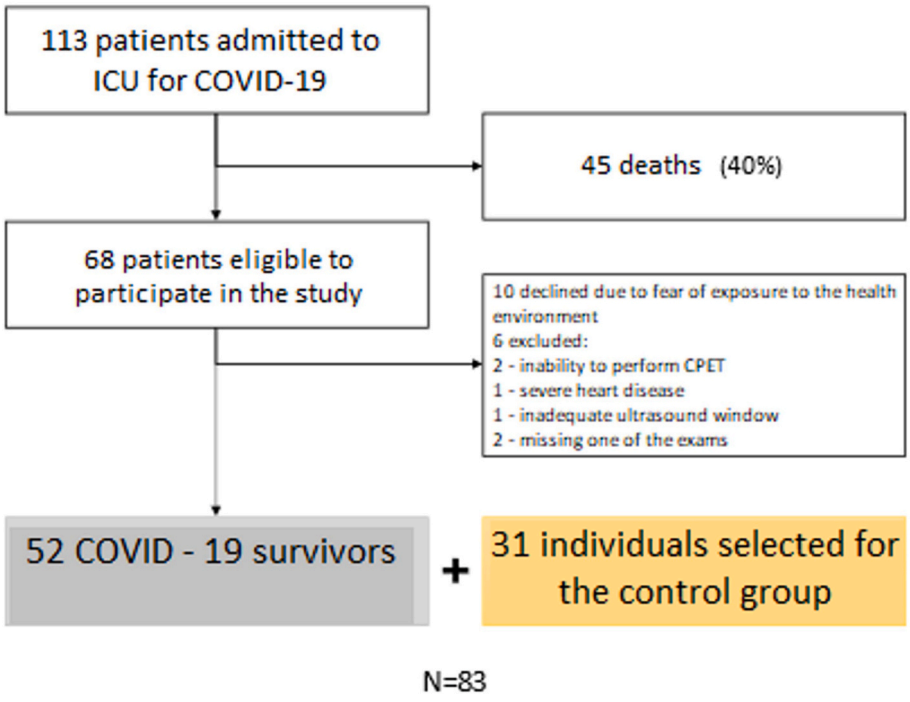


Fig. 1. Flowchart of patient inclusion in the research. (ICU: Intensive Care Unit; COVID-19: Coronavirus-19 infection. CPET: Cardiopulmonary exercise test).

frequent in both the COVID and control groups was the presence of hypertension (27 vs. 19 %; p = 0.597). None of the participants were using more than 2 classes of drugs as antihypertensive treatment. Patients with COVID-19 had higher SBP and DBP.

The median laboratory values upon admission to the ICU in the COVID-19 group were as follows: oxygenation index of 101.5 mmHg (95 % CI, 81–133.5), troponin I of 18.1 pg/mL (95 % CI, 9.1–58.8), lactic dehydrogenase of 723 U/L (95 % CI, 453–1027); C-reactive protein of 128 mg/L (95 % CI, 73.5–153); D-dimer of 905 μg/L (95 % CI, 315–2550.5); and lymphocytes of 1285 cells/mm3 (95 % CI, 841.5–1561.7). Thirty-one (60 %) patients required invasive mechanical ventilation, with an average duration of 6 days of invasive ventilation, and the hospital stay was mostly between 11 and 20 days. During the study period, we lacked access to novel antiviral medications, such as remdesivir. Given that all our patients received ventilatory support, the established treatment protocol encompassed systemic corticosteroid therapy for all. Among patients who required invasive mechanical ventilation, one patient received extracorporeal membrane oxygenation (ECMO) support, and this patient's total length of hospitalization was 80 days. Patients with COVID-19 were evaluated on average 83 ± 30 days after hospital discharge. All received assistance in the form of a rehabilitation program after discharge.

Table 2
Characteristics of the echocardiogram and cardiopulmonary exercise test of the patients.

Echocardiogram	COVID-19 (n = 52)	Control (n = 31)	p value
LVEDD indexed (mm/m^2)	26.5 ± 8.7	25.5 ± 7.5	0.611
LV indexed mass (g/m^2)	75.0 ± 18.1	72.4 ± 18.0	0.529
LAVI (mL/m^2)	24.6 ± 6.4	26,5 ± 7,8	0.237
E/e'	6.8 ± 1.2	6.7 ± 1.5	0.838
Tricuspid S' (cm/s)	13.4 ± 2.1	13.3 ± 1.8	0.934
TAPSE (mm)	21.5 ± 3.3	22.8 ± 3.3	0.098
sPAP (mmHg)	22.1 ± 4.9	21.7 ± 5.5	0.784
TRV (m/s)	2.2 ± 0.3	2.0 ± 0.3	0.011
LVEF (%)	62 ± 7	66 ± 6	0.007
LVGLS (%)	−18.7 ± 2.6	−20.4 ± 1.4	0.001
GWI (mmHg)	2308 ± 464	2253 ± 358	0.571
GCW (mmHg)	2515 ± 458	2442 ± 315	0.440
GWW (mmHg)	152 ± 81	101 ± 54	0.003
GWE (%)	93 ± 3	95 ± 2	0.002
Cardiopulmonary exercise test			
Peak VO_2 (mL/min/kg)	24.4 ± 5.4	33.4 ± 8.8	<0.001
Peak VO_2 (% pred)	92 ± 20	112 ± 21	<0.001
Work (watts)	227 ± 61	242 ± 81	<0.001
RER	1.12 ± 0.09	1.18 ± 0.09	0.01
Peak HR (bpm)	160 ± 14	176 ± 11	<0.001
VO_2/HR (mL/beats·min)	13.2 ± 4.1	14.6 ± 4.2	0.151
VO_2/HR (% pred)	96 ± 21	104 ± 23	0.103
Peak Ve (L/min)	84.6 ± 22.6	104.9 ± 27	<0.001
Breathing reserve (%)	29 ± 13	20 ± 13	0.014
Slope Ve/VCO_2	33.1 ± 5.9	33.5 ± 5.1	0.794
OUES (L/min)	2.3 ± 0.7	2.5 ± 0.7	0.147
OUES% (% of pred.)	89 ± 16	102 ± 22	0.002
$T_{1/2}$ (s)	120.3 ± 32	97.6 ± 27	0.002
HRR at 1 min (bpm)	−20 ± 10	−23 ± 15	0.265
HRR at 2 min (bpm)	−36 ± 11	−43 ± 13	0.010

E/e': ratio between the peak of the mitral and tissue E wave; GCW: global constructive work; GWE: global work efficiency; GWI: global work index; GWW: global wasted work; HR: heart rate; HRR: heart rate decay in recovery from exertion; HR/VO_2: relationship between heart rate and oxygen consumption; LAVI: left atrial volume index; LVEDD: left ventricle end-diastolic diameter; LVEF: left ventricle ejection fraction by Simpson; LVGLS: left ventricle global longitudinal strain; OUES: oxygen uptake efficiency slope; RER: respiratory exchange ratio (VCO_2/VO_2); Slope Ve/VCO_2: slope of the ratio of minute ventilation and carbon dioxide production; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity; Ve: minute ventilation; VO_2: oxygen consumption; T ½: recovery time for VO_2 to drop to 50 % of its peak value.

3.2. Echocardiographic features

The echocardiographic characteristics are presented in Table 2. There were no significant differences in morphological parameters between the groups. The Doppler method revealed a significant difference in tricuspid regurgitation velocity. Of the LV functional parameters, there were significant differences observed in ejection fraction, LVGLS, GWW and GWE (Figs. 2–3).

3.3. Exercise evaluation

The CPET results are presented in Tables 2 and in Fig. 4. The two groups differed in peak VO_2, HR, Ve and RER. They also significantly differed in the number of patients with desaturation (14 vs. 0; p = 0.002). Although there was no significant difference in their oxygen pulse values (HR/VO_2), the morphology of the curve (dynamic behaviour) was significantly altered, with the finding of an early plateau in the COVID-19 group (14 vs. 0; p = 0.002). Regarding oxygen kinetics, there was a significant difference in relation to OUES% and T ½. During recovery, there was a significant difference in the drop-in heart rate (HRR), which was better characterized in the second minute of recovery than in the first minute. The chronotropic index was lower for patients with COVID-19 than for controls (0.83 ± 0.20 vs. 1.03 ± 0.15; p < 0.0001).

3.4. Association between echocardiographic and spiroergometric results

In Fig. 5, we present the main correlations between the echocardiogram data and the CPET results. There was an association between higher GWW and the following CPET results: deficit in peak VO_2 from predicted (r = −0.36; p = 0.001), reduction in minute ventilation (r = −0.30; p = 0.008), deficit in VO_2/HR from predicted (r = −0.32; p = 0.004), and HRR at 2 min (r = −0.28; p = 0.012). There was also a correlation between increased GWE and increased peak VO_2 in % predicted (r = 0.31; p = 0.004). None of the other echocardiographic variables showed a significant correlation with CPET data.

4. Discussion

The main findings of this study revealed that most severe COVID-19 patients exhibited low LVGLS and GWE, accompanied by high GWW. They demonstrated lower exercise capacity, as evidenced by lower peak VO_2, lower work achieved, and lower OUES% than the matched controls. These patients exhibited a prolonged time for heart rate recovery, as indicated by higher $T_{1/2}$ and higher HRR at 2 min.

Since early studies involving MW and COVID-19, GWE has emerged as a crucial marker of subclinical cardiac dysfunction in hospitalized patients [12,27]. It has been investigated as a prognostic indicator of in-hospital mortality, even in those with normal LVEF [28,29]. In our study, although there were significant differences in LVEF between the groups, these values still fell within the normal range, having no clinical significance. Regarding MW, patients exhibited normal GWI values. This finding could be attributed to the timing of the examination (an average of 60 days after hospital discharge, with cardiac rehabilitation), the patients' higher systolic blood pressure than the control group, the younger age of the patients compared to previously published studies, or survivor bias [30]. In our study, the patients demonstrated higher values of GWW and lower values of GWE and LVGLS, indicating the presence of subclinical cardiac dysfunction in patients with COVID-19. Some studies have suggested an improvement in some of these indices, particularly GWI and particularly in the acute phase [31]. However, there are still no prospective studies evaluating these parameters specifically related to COVID-19.

Despite the considerable heterogeneity among studies, aerobic capacity is often reduced in patients following COVID-19, significantly improving in the months of recovery from the acute phase [32–34].

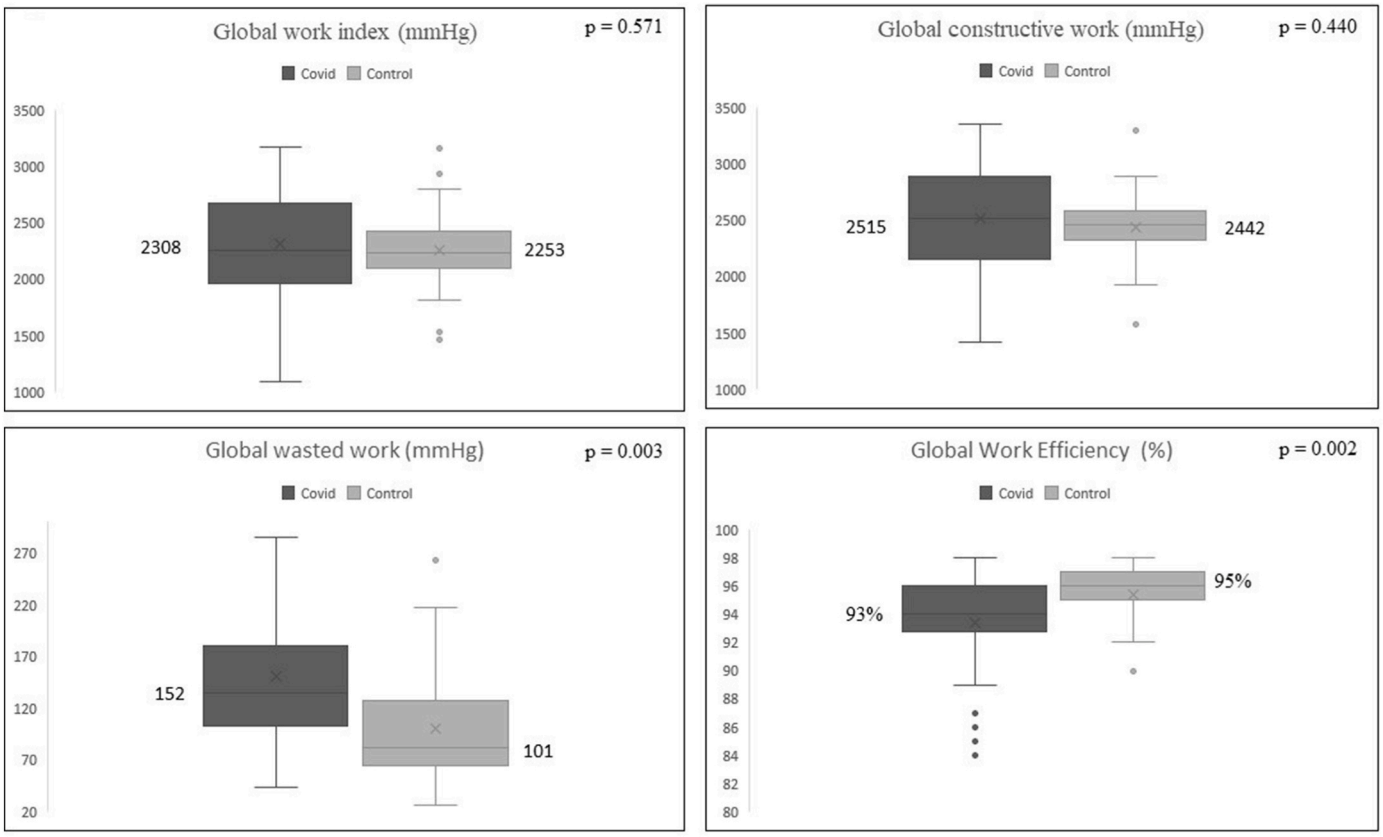


Fig. 2. Comparison of myocardial work between COVID-19 and Control groups.

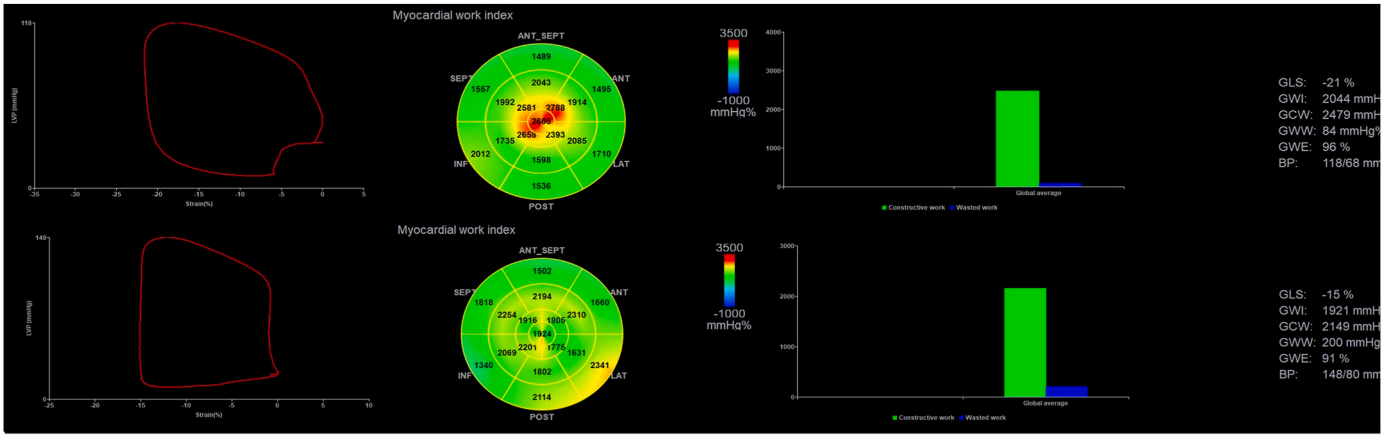


Fig. 3. Myocardial work index bull's-eye mapping. (A) Representative patient of the control group with normal strain and myocardial work; (B) Representative patient of COVID-19 group with severe reduced global longitudinal strain, myocardial work index, and work efficiency.

Among the multiple factors underlying this, peripheral limitation has been considered the primary mechanism associated with anaemia, reduced oxygen extraction, impaired mechanical efficiency, and decreased muscle strength [35–38]. In a study assessing the long-term evolution of aerobic capacity over the first year after COVID-19, the number of patients with cardiocirculatory limitation was even higher than that of patients with ventilatory limitation [17].

The persistence of reduced VO_2 in a significant portion of patients, even after a long period of recovery, suggests that peripheral deconditioning alone does not explain this reduction. While there is no clear central cardiocirculatory mechanism (e.g., myocardial contractility deficit), there is a strong association between low VO_2 and the presence of diastolic dysfunction, chronotropic incompetence, autonomic dysfunction, and peripheral vascular damage (i.e., endothelial dysfunction), which can limit oxygen delivery to muscles during exercise [39–41]. One way to assess autonomic dysfunction is through heart rate decline in the recovery phase, and chronotropic incompetence has been seen in association with an abnormal heart rate response during recovery [42–45]. In our study, patients exhibited a blunted peak heart rate, increased $T_{1/2}$, and reduced HRR in the second minute compared to the control group, potentially indicating impaired parasympathetic drive and possibly having prognostic implications for the reduced aerobic capacity of such patients, as high heart rate variability is a marker of a favourable chronotropic adaptation response seen in healthy individuals.

Previous studies have suggested evidence of mitochondrial

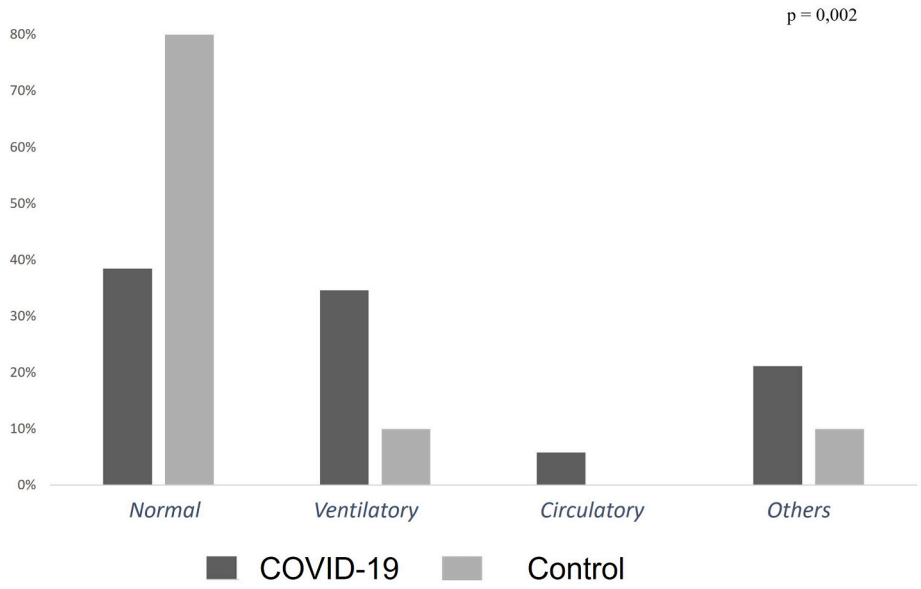


Fig. 4. Exercise capacity between COVID-19 and Control.

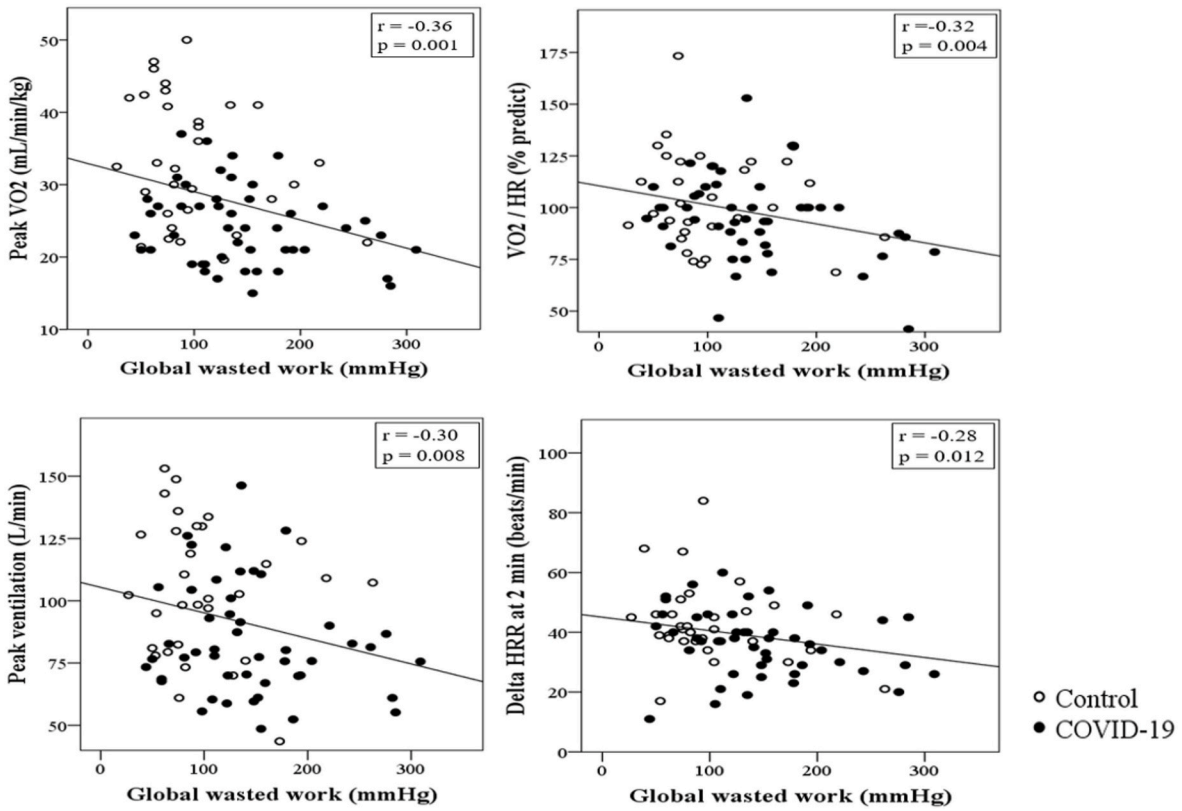


Fig. 5. Correlations between echocardiogram and CPET data.

dysfunction characterized by significant impairment in fat beta-oxidation and increased blood lactate accumulation during exercise in patients with post-acute sequelae of SARS-CoV-2 infection [46]. Furthermore, patients with COVID-19 exhibit exaggerated muscle sympathetic nerve activity and a blunted vasodilatory response to mental challenge compared to control adults [30]. Taken together, these alterations may contribute to exercise limitations in these patients.

To our knowledge, this is the first study to evaluate cardiac mechanics via myocardial work and establish correlations with CPET in patients who have recuperated from severe COVID-19. Shimoni et al. had previously demonstrated the association between reduced LVGLS and aerobic capacity assessed through the standard treadmill exercise stress test using the Bruce protocol. Although it was weak, we found an association between higher wasted myocardial work (GWW) and lower VO_2% and an association between higher myocardial work efficiency (GWE) and higher peak VO_2 values. GWE reflects regional myocardial oxygen metabolism when compared against measurements obtained by positron emission tomography using (18F) fluorodeoxyglucose [47,48].

Therefore, the reduction in GWE does not exclude a central cardiocirculatory component related to disturbances in myocardial metabolism that may occur in the context of increased systemic inflammation and may contribute to the reduced aerobic capacity of these patients.

Our study has some limitations. First, all patients had severe COVID-19 requiring ICU admission, so our findings may not be applicable to patients with long COVID outside this profile. Our patients had not received the COVID-19 vaccine due to the timing of the study, so our findings may not replicate in a vaccinated population. Another noteworthy aspect pertains to the control group. Given the stage of the pandemic during the study, we were unable to perform RT−PCR testing for COVID-19 in the control group, as the Brazilian Ministry of Health protocol did not include testing for asymptomatic individuals. Therefore, we cannot exclude the possibility that some of the control group had asymptomatic COVID-19, which may still affect cardiovascular capacity. Another significant limitation in our study was the absence of a control group consisting of critically ill patients but with a different infectious cause other than COVID-19. Consequently, we cannot solely attribute the observed alterations in results to COVID-19 or to post-ICU care syndrome. Furthermore, we had no data on the patients' aerobic capacity prior to hospitalization, and since all the patients underwent cardiopulmonary rehabilitation, we cannot assess the impact of this intervention on their recovery. Cardiac output, arterial lactate and endothelial function were not assessed during exercise, and muscle biopsies were not conducted, which introduces some uncertainty in evaluating the degree of deconditioning.

5. Conclusion

Survivors of severe COVID-19 exhibit increased wasted work, with lower myocardial efficiency, significantly reduced aerobic exercise capacity, and abnormal heart rate response during recovery, which may be related to previously described late symptoms. The reduction in functional capacity during physical exercise is partly associated with a decrease in resting myocardial work efficiency. These findings strongly indicate the need to determine whether these manifestations persist in the long term and their impact on cardiovascular health and quality of life in COVID-19 survivors.

CRediT authorship contribution statement

Thiago Lins Fagundes de Sousa: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Allan Robson Kluser Sales:** Resources, Data curation. **Juliana Góes Martins Fagundes:** Writing – review & editing, Writing – original draft. **Luis Fábio Barbosa Botelho:** Software, Formal analysis. **Francis Ribeiro de Souza:** Conceptualization, Formal analysis, Writing – review & editing. **Guilherme Wesley Fonseca:** Writing – review & editing, Software, Formal analysis, Data curation. **André Luis Pereira de Albuquerque:** Methodology, Investigation, Data curation. **Marcelo Dantas Tavares de Melo:** Writing – review & editing, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Maria-Janieire de Nazaré Nunes Alves:** Writing – review & editing, Supervision, Project administration, Data curation.

References

[1] F. Catapano, L. Marchitelli, G. Cundari, F. Cilia, G. Mancuso, G. Pambianchi, N. Galea, P. Ricci, C. Catalano, M. Francone, Role of advanced imaging in COVID-19 cardiovascular complications, Insights into Imaging 12 (2021), https://doi.org/10.1186/s13244-021-00973-z.

[2] A.S. Ali, D. Sheikh, T.R. Chandler, S. Furmanek, J. Huang, J.A. Ramirez, F. Arnold, R. Cavallazzi, Cardiovascular complications are the primary drivers of mortality in hospitalized patients with SARS-CoV-2 community-acquired pneumonia, Chest 163 (2023) 1051–1060, https://doi.org/10.1016/j.chest.2022.11.013.

[3] P.O. Guimarães, F.R. de Souza, R.D. Lopes, C. Bittar, F.A. Cardozo, B. Caramelli, D. Calderaro, C.P. Albuquerque, L.F. Drager, F. Feres, L. Baracioli, G. Feitosa Filho, R.R. Barbosa, H.B. Ribeiro, E. Ribeiro, R.J. Alves, A. Soeiro, B. Faillace, E. Figueiredo, L.P. Damiani, R.M. do Val, N. Huemer, L.G. Nicolai, L.A. Hajjar, A. Abizaid, R. Kalil Filho, High risk coronavirus disease 2019: the primary results of the CoronaHeart multi-center cohort study, IJC Heart & Vasculature 36 (2021) 100853, https://doi.org/10.1016/j.ijcha.2021.100853.

[4] F. Kwenandar, K.V. Japar, V. Damay, T.I. Hariyanto, M. Tanaka, N.P.H. Lugito, A. Kurniawan, Coronavirus disease 2019 and cardiovascular system: a narrative review, IJC Heart and Vasculature 29 (2020), https://doi.org/10.1016/j.ijcha.2020.100557.

[5] M. L'Heureux, M. Sternberg, L. Brath, J. Turlington, M.G. Kashiouris, Sepsis-induced cardiomyopathy: a comprehensive review, Curr. Cardiol. Rep. 22 (2020), https://doi.org/10.1007/s11886-020-01277-2.

[6] L. Wu, A.M. O'Kane, H. Peng, Y. Bi, D. Motriuk-Smith, J. Ren, SARS-CoV-2 and cardiovascular complications: from molecular mechanisms to pharmaceutical management, Biochem. Pharmacol. 178 (2020), https://doi.org/10.1016/j.bcp.2020.114114.

[7] V.O. Puntmann, M.L. Carerj, I. Wieters, M. Fahim, C. Arendt, J. Hoffmann, A. Shchendrygina, F. Escher, M. Vasa-Nicotera, A.M. Zeiher, M. Vehreschild, E. Nagel, Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19), JAMA Cardiology 5 (2020) 1265–1273, https://doi.org/10.1001/jamacardio.2020.3557.

[8] O. Shimoni, R. Korenfeld, S. Goland, V. Meledin, D. Haberman, J. George, S. Shimoni, Subclinical myocardial dysfunction in patients recovered from COVID-19 disease: correlation with exercise capacity, Biology 10 (2021) 1201, https://doi.org/10.3390/biology10111201.

[9] W.E. Moody, B. Liu, H.M. Mahmoud-Elsayed, J. Senior, S.S. Lalla, A.M. Khan-Kheil, S. Brown, A. Saif, A. Moss, W.M. Bradlow, J. Khoo, M. Ahamed, C. McAloon, S. S. Hothi, R.P. Steeds, Persisting adverse ventricular remodeling in COVID-19 survivors: a longitudinal echocardiographic study, J. Am. Soc. Echocardiogr. 34 (2021) 562–566, https://doi.org/10.1016/j.echo.2021.01.020.

[10] J. Chan, N.F.A. Edwards, G.M. Scalia, B.K. Khandheria, Myocardial work: a new type of strain imaging? J. Am. Soc. Echocardiogr. 33 (2020) 1209–1211, https://doi.org/10.1016/j.echo.2020.05.004.

[11] S. Roemer, A. Jaglan, D. Santos, M. Umland, R. Jain, A.J. Tajik, B.K. Khandheria, The utility of myocardial work in clinical practice, J. Am. Soc. Echocardiogr. 34 (2021) 807–818, https://doi.org/10.1016/j.echo.2021.04.013.

[12] A. Jaglan, S. Roemer, M.F. Jan, B.K. Khandheria, Myocardial work index: a glimmer of hope in COVID-19, European Heart Journal Cardiovascular Imaging 22 (2021) 228, https://doi.org/10.1093/ehjci/jeaa181.

[13] A. Hubert, V. Le Rolle, C. Leclercq, E. Galli, E. Samset, C. Casset, P. Mabo, A. Hernandez, E. Donal, Estimation of myocardial work from pressure–strain loops analysis: an experimental evaluation, European Heart Journal Cardiovascular Imaging 19 (2018) 1372–1379, https://doi.org/10.1093/ehjci/jey024.

[14] M.P. Cassar, E.M. Tunnicliffe, N. Petousi, A.J. Lewandowski, C. Xie, M. Mahmod, A. H.A. Samat, R.A. Evans, C.E. Brightling, L.-P. Ho, S.K. Piechnik, N.P. Talbot, D. Holdsworth, V.M. Ferreira, S. Neubauer, B. Raman, Symptom persistence despite improvement in cardiopulmonary health - insights from longitudinal CMR, CPET and lung function testing post-COVID-19, EClinicalMedicine 41 (2021) 101159, https://doi.org/10.1016/j.eclinm.2021.101159.

[15] A. Mohr, L. Dannerbeck, T.J. Lange, M. Pfeifer, S. Blaas, B. Salzberger, F. Hitzenbichler, M. Koch, Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19, Multidiscip Respir Med 16 (2021) 732, https://doi.org/10.4081/mrm.2021.732.

[16] R.F. Rinaldo, M. Mondoni, E.M. Parazzini, F. Pitari, E. Brambilla, S. Luraschi, M. Balbi, G.F. Sferrazza Papa, G. Sotgiu, M. Guazzi, F. Di Marco, S. Centanni, Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors, Eur. Respir. J. 58 (2021) 2100870, https://doi.org/10.1183/13993003.00870-2021.

[17] C.B. Ingul, A. Edvardsen, T. Follestad, D. Trebinjac, O.A.W. Ankerstjerne, E. Brønstad, Ø. Rasch-Halvorsen, B. Aarli, H. Dalen, B.M. Nes, T.V. Lerum, G. Einvik, K. Stavem, I. Skjørten, Changes in cardiopulmonary exercise capacity and limitations 3–12 months after COVID-19, Eur. Respir. J. 61 (2023) 2200745, https://doi.org/10.1183/13993003.00745-2022.

[18] M. Francone, F. Iafrate, G.M. Masci, S. Coco, F. Cilia, L. Manganaro, V. Panebianco, C. Andreoli, M.C. Colaiacomo, M.A. Zingaropoli, M.R. Ciardi, C.M. Mastroianni, F. Pugliese, F. Alessandri, O. Turriziani, P. Ricci, C. Catalano, Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis, Eur. Radiol. 30 (2020) 6808–6817, https://doi.org/10.1007/s00330-020-07033-y.

[19] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.-U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (2015) 1–39.e14, https://doi.org/10.1016/j.echo.2014.10.003.

[20] K Wasserman, J Hansen, D Sue, W Stringer, B Whipp, eds, Principles of Exercise Testing and Interpretation, fourth ed., Lippincott Williams & Wilkins, Philadelphia, USA, (n.d).

[21] J. Chan, N.F.A. Edwards, B.K. Khandheria, K. Shiino, S. Sabapathy, B. Anderson, R. Chamberlain, G.M. Scalia, A new approach to assess myocardial work by non-invasive left ventricular pressure-strain relations in hypertension and dilated cardiomyopathy, European Heart Journal Cardiovascular Imaging 20 (2019) 31–39, https://doi.org/10.1093/ehjci/jey131.

[22] R. Manganaro, S. Marchetta, R. Dulgheru, F. Ilardi, T. Sugimoto, S. Robinet, S. Cimino, Y.Y. Go, A. Bernard, G. Kacharava, G.D. Athanassopoulos, D. Barone, M. Baroni, N. Cardim, A. Hagendorff, K. Hristova, T. López-Fernández, G. De La

Morena, B.A. Popescu, M. Penicka, T. Ozyigit, J.D. Rodrigo Carbonero, N. Van De Veire, R.S. Von Bardeleben, D. Vinereanu, J.L. Zamorano, M. Rosca, A. Calin, M. Moonen, J. Magne, B. Cosyns, E. Galli, E. Donal, S. Carerj, C. Zito, C. Santoro, M. Galderisi, L.P. Badano, R.M. Lang, C. Oury, P. Lancellotti, Echocardiographic reference ranges for normal non-invasive myocardial work indices: results from the EACVI NORRE study, European Heart Journal Cardiovascular Imaging 20 (2019) 582–590, https://doi.org/10.1093/ehjci/jey188.

[23] J. Porszasz, R. Casaburi, A. Somfay, L.J. Woodhouse, B.J. Whipp, A treadmill ramp protocol using simultaneous changes in speed and grade, Med. Sci. Sports Exerc. 35 (2003) 1596–1603, https://doi.org/10.1249/01.MSS.0000084593.56786.DA.

[24] Carlos Alberto de Castro Pereira, José Manoel Jansen, Sérgio S. Menna Barreto, Jamocyr Marinho, Nara Sulmonett, Ricardo Marques Dias, Sérgio Roberto Nassif, Diretrizes para o teste de função pulmonar, J. Bras. Pneumol. 28:suplemento 3 (n. d.).

[25] J.E. Hansen, D.Y. Sue, K. Wasserman, Predicted values for clinical exercise testing, Am. Rev. Respir. Dis. 129 (1984) S49–S55, https://doi.org/10.1164/arrd.1984.129.2P2.S49.

[26] M. Hollenberg, I.B. Tager, Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise, J. Am. Coll. Cardiol. 36 (2000) 194–201, https://doi.org/10.1016/s0735-1097(00)00691-4.

[27] O. Lairez, V. Blanchard, V. Houard, F. Vardon-Bounes, M. Lemasle, E. Cariou, Y. Lavie-Badie, S. Ruiz, S. Cazalbou, C. Delmas, B. Georges, M. Galinier, D. Carrié, J.M. Conil, V. Minville, Cardiac imaging phenotype in patients with coronavirus disease 2019 (COVID-19): results of the cocarde study, Int. J. Cardiovasc. Imag. 37 (2021) 449–457, https://doi.org/10.1007/s10554-020-02010-4.

[28] A.S. Minhas, N.A. Gilotra, E. Goerlich, T. Metkus, B.T. Garibaldi, G. Sharma, N. Bavaro, S. Phillip, E.D. Michos, A.G. Hays, Myocardial work efficiency, A novel measure of myocardial dysfunction, is reduced in COVID-19 patients and associated with in-hospital mortality, Frontiers in Cardiovascular Medicine 8 (2021). https://www.frontiersin.org/articles/10.3389/fcvm.2021.667721. (Accessed 27 May 2023).

[29] F.J. Olsen, M.C.H. Lassen, K.G. Skaarup, J. Christensen, F.S. Davidovski, A. S. Alhakak, M. Sengeløv, A.B. Nielsen, N.D. Johansen, C. Graff, H. Bundgaard, C. Hassager, R. Jabbari, J. Carlsen, O. Kirk, M.G. Lindholm, L. Wiese, O. P. Kristiansen, O.W. Nielsen, B. Lindegaard, N. Tønder, C.S. Ulrik, M. Lamberts, P. Sivapalan, G. Gislason, K. Iversen, J.U.S. Jensen, M. Schou, J.H. Svendsen, J. M. Aalen, O.A. Smiseth, E.W. Remme, T. Biering-Sørensen, Myocardial work in patients hospitalized with COVID-19: relation to biomarkers, COVID-19 severity, and all-cause mortality, J. Am. Heart Assoc. 11 (2022) e026571, https://doi.org/10.1161/JAHA.122.026571.

[30] D. Faria, R. Moll-Bernardes, L. Testa, C.M.V. Moniz, E.C. Rodrigues, J.M. Mota, F. R. Souza, M.J.N.N. Alves, B.E. Ono, J.E. Izaias, A.O. Sales, T.S. Rodrigues, V.M. C. Salemi, C.P. Jordão, K. De Angelis, D.H. Craighead, M.J. Rossman, L. A. Bortolotto, F.M. Consolim-Colombo, M.C.C. Irigoyen, D.R. Seals, C.E. Negrão, A. R.K. Sales, Neurovascular and hemodynamic responses to mental stress and exercise in severe COVID-19 survivors, Am. J. Physiol. Regul. Integr. Comp. Physiol. 325 (2023) R269–R279, https://doi.org/10.1152/ajpregu.00111.2023.

[31] I. Ikonomidis, V. Lambadiari, A. Mitrakou, A. Kountouri, K. Katogiannis, J. Thymis, E. Korakas, G. Pavlidis, P. Kazakou, G. Panagopoulos, I. Andreadou, C. Chania, A. Raptis, A. Bamias, K. Thomas, P. Kazakou, S. Grigoropoulou, D. Kavatha, A. Antoniadou, M.A. Dimopoulos, G. Filippatos, Myocardial work and vascular dysfunction are partially improved at 12 months after COVID-19 infection, Eur. J. Heart Fail. 24 (2022) 727–729, https://doi.org/10.1002/ejhf.2451.

[32] M.S. Durstenfeld, K. Sun, P. Tahir, M.J. Peluso, S.G. Deeks, M.A. Aras, D.J. Grandis, C.S. Long, A. Beatty, P.Y. Hsue, Use of cardiopulmonary exercise testing to evaluate long COVID-19 symptoms in adults: a systematic review and meta-analysis, JAMA Netw. Open 5 (2022) e2236057, https://doi.org/10.1001/jamanetworkopen.2022.36057.

[33] D.M. Mancini, D.L. Brunjes, A. Lala, M.G. Trivieri, J.P. Contreras, B.H. Natelson, Use of cardiopulmonary stress testing for patients with unexplained dyspnea post-coronavirus disease, JACC Heart Fail 9 (2021) 927–937, https://doi.org/10.1016/j.jchf.2021.10.002.

[34] E. Pleguezuelos, A. Del Carmen, G. Llorensi, J. Carcole, P. Casarramona, E. Moreno, P. Ortega, M. Serra-Prat, E. Palomera, M.M. Miravitlles, J.C. Yebenes, R. Boixeda, L. Campins, K. Villelabeitia-Jaureguizar, M.V. Garnacho-Castaño, Severe loss of mechanical efficiency in COVID-19 patients, Journal of Cachexia, Sarcopenia and Muscle 12 (2021) 1056–1063, https://doi.org/10.1002/jcsm.12739.

[35] C. Baratto, S. Caravita, A. Faini, G.B. Perego, M. Senni, L.P. Badano, G. Parati, Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study, J. Appl. Physiol. 130 (2021) 1470–1478, https://doi.org/10.1152/japplphysiol.00710.2020.

[36] P. Clavario, V.D. Marzo, R. Lotti, C. Barbara, A. Porcile, C. Russo, F. Beccaria, M. Bonavia, L.C. Bottaro, M. Caltabellotta, F. Chioni, M. Santangelo, A.J. Hautala, P. Ameri, M. Canepa, I. Porto, Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up. https://doi.org/10.1101/2020.11.15.20231985, 2020.

[37] P. Clavario, V. De Marzo, R. Lotti, C. Barbara, A. Porcile, C. Russo, F. Beccaria, M. Bonavia, L.C. Bottaro, M. Caltabellotta, F. Chioni, M. Santangelo, A.J. Hautala, R. Griffo, G. Parati, U. Corrà, I. Porto, Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up, Int. J. Cardiol. 340 (2021) 113–118, https://doi.org/10.1016/j.ijcard.2021.07.033.

[38] I. Singh, P. Joseph, P.M. Heerdt, M. Cullinan, D.D. Lutchmansingh, M. Gulati, J. D. Possick, D.M. Systrom, A.B. Waxman, Persistent exertional intolerance after COVID-19: insights from invasive cardiopulmonary exercise testing, Chest 161 (2022) 54–63, https://doi.org/10.1016/j.chest.2021.08.010.

[39] I. Longobardi, D.M.L. do Prado, K.F. Goessler, M.M. Meletti, G.N. de Oliveira Júnior, D.C.O. de Andrade, B. Gualano, H. Roschel, Oxygen uptake kinetics and chronotropic responses to exercise are impaired in survivors of severe COVID-19, Am. J. Physiol. Heart Circ. Physiol. 323 (2022) H569–H576, https://doi.org/10.1152/ajpheart.00291.2022.

[40] Á. Aparisi, R. Ladrón, C. Ybarra-Falcón, J. Tobar, J.A. San Román, Exercise intolerance in post-acute sequelae of COVID-19 and the value of cardiopulmonary exercise testing- a mini-review, Front. Med. 9 (2022). https://www.frontiersin.org/articles/10.3389/fmed.2022.924819. (Accessed 27 May 2023).

[41] C. Serviente, S.T. Decker, G. Layec, From heart to muscle: pathophysiological mechanisms underlying long-term physical sequelae from SARS-CoV-2 infection, J. Appl. Physiol. 132 (2022) 581–592, https://doi.org/10.1152/japplphysiol.00734.2021.

[42] F. Schwendinger, R. Knaier, T. Radtke, A. Schmidt-Trucksäss, Low cardiorespiratory fitness post-COVID-19: a narrative review, Sports Med. 53 (2023) 51–74, https://doi.org/10.1007/s40279-022-01751-7.

[43] D. Faria, R.J. Moll-Bernardes, L. Testa, C.M.V. Moniz, E.C. Rodrigues, A. G. Rodrigues, A. Araujo, M.J.N.N. Alves, B.E. Ono, J.E. Izaias, V.M.C. Salemi, C. P. Jordão, G. Amaro-Vicente, M.U.P.B. Rondon, K.R. Ludwig, D.H. Craighead, M. J. Rossman, F.M. Consolim-Colombo, K.D. Angelis, M.C.C. Irigoyen, D.R. Seals, C. E. Negrão, A.R.K. Sales, Sympathetic neural overdrive, aortic stiffening, endothelial dysfunction, and impaired exercise capacity in severe COVID-19 survivors: a mid-term study of cardiovascular sequelae, Hypertension (2023), https://doi.org/10.1161/HYPERTENSIONAHA.122.19958.

[44] C.M. Ribeiro, R. de A. Gomes, C.B. de M. Monteiro, R.M. Dias, A.O. Simcsik, L.V. de Araújo, L.C.P. Maia, A.P. de Oliveira, B.L. de Freitas, H. Dawes, C. Ferreira, Í.A. P. de Moraes, T.D. da Silva, Heart rate variability during virtual reality activity in individuals after hospitalization for COVID-19: a cross-sectional control study, Electronics 12 (2023) 1925, https://doi.org/10.3390/electronics12081925.

[45] K. Shetler, R. Marcus, V.F. Froelicher, S. Vora, D. Kalisetti, M. Prakash, D. Do, J. Myers, Heart rate recovery: validation and methodologic issues, J. Am. Coll. Cardiol. 38 (2001) 1980–1987, https://doi.org/10.1016/S0735-1097(01)01652-7.

[46] E. de Boer, I. Petrache, N.M. Goldstein, J.T. Olin, R.C. Keith, B. Modena, M.P. Mohning, Z.X. Yunt, I. San-Millán, J.J. Swigris, 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 (n.d.) 126–129. https://doi.org/10.1164/rccm.202108-1903LE.

[47] K. Russell, M. Eriksen, L. Aaberge, N. Wilhelmsen, H. Skulstad, E.W. Remme, K. H. Haugaa, A. Opdahl, J.G. Fjeld, O. Gjesdal, T. Edvardsen, O.A. Smiseth, A novel clinical method for quantification of regional left ventricular pressure–strain loop area: a non-invasive index of myocardial work, Eur. Heart J. 33 (2012) 724–733, https://doi.org/10.1093/eurheartj/ehs016.

[48] J.J. Patel, T. Alzahrani, Myocardial perfusion scan, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2023. http://www.ncbi.nlm.nih.gov/books/NBK539772/. (Accessed 28 May 2023).