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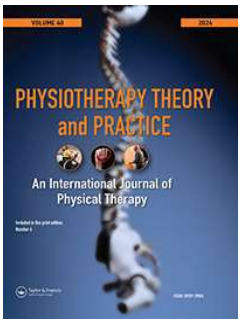

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RESEARCH REPORT

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Comparison of the muscle oxygenation during submaximal and maximal exercise tests in patients post-coronavirus disease 2019 syndrome with pulmonary involvement

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ABSTRACT

Introduction: Pulmonary involvement is prevalent in patients with coronavirus disease 2019 (COVID-19). Arterial hypoxemia may reduce oxygen transferred to the skeletal muscles, possibly leading to impaired exercise capacity. Oxygen uptake may vary depending on the increased oxygen demand of the muscles during submaximal and maximal exercise.

Objective: This study aimed to compare muscle oxygenation during submaximal and maximal exercise tests in patients with post-COVID-19 syndrome with pulmonary involvement.

Methods: Thirty-nine patients were included. Pulmonary function (spirometry), peripheral muscle strength (dynamometer), quadriceps femoris (QF) muscle oxygenation (Moxy® device), and submaximal exercise capacity (six-minute walk test (6-MWT)) were tested on the first day, maximal exercise capacity (cardiopulmonary exercise test (CPET)) was tested on the second day. Physical activity level was evaluated using an activity monitor worn for five consecutive days. Cardiopulmonary responses and muscle oxygenation were compared during 6-MWT and CPET.

Results: Patients' minimum and recovery muscle oxygen saturation were significantly decreased; maximum total hemoglobin increased, heart rate, blood pressure, breathing frequency, dyspnea, fatigue, and leg fatigue at the end-of-test and recovery increased in CPET compared to 6-MWT ($p < .050$). Peak oxygen consumption (VO_{2peak}) was 18.15 ± 4.75 ml/min/kg, VO_{2peak}; percent predicted < 80% was measured in 51.28% patients. Six-MWT distance and QF muscle strength were less than 80% predicted in 58.9% and 76.9% patients, respectively.

Conclusions: In patients with post-COVID-19 syndrome with pulmonary involvement, muscle deoxygenation of QF is greater during maximal exercise than during submaximal exercise. Specifically, patients with lung impairment should be evaluated for deoxygenation and should be taken into consideration during pulmonary rehabilitation.

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COVID-19; exercise test; oxygen saturation

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has spread rapidly all over the world (Hu, Guo, Zhou, and Shi, 2021). COVID-19 is a multi-organ disease, and the severity of the disease ranges from mild to very serious (Zaim, Chong, Sankaranarayanan, and Harky, 2020). Various symptoms occur depending on the severity of the disease in the acute, post-acute, and chronic term. Long-term symptoms are prevalent in more than 60% of patients infected by COVID-19 (Fernández-de-Las- Peñas et al., 2021). The Centers for Disease Control and Prevention defines post-COVID conditions as failure to improve after the 4-week acute phase. However, many patients continue to improve between 4 and 12 weeks (Centers for Disease Control and Prevention, 2023). Long-term symptoms include fatigue, dyspnea, impaired exercise capacity, and lung function; however, the symptoms are not limited to only these (Nalbandian et al., 2021; Raman et al., 2021). All these symptoms are associated with widespread ground glass opacities on computed chest tomography scans and radiography (Kang, Li, and Zhou, 2020; Toussie et al., 2020). It is essential to understand the physiological mechanisms underlying persistent dyspnea, fatigue, and impaired exercise capacity after COVID-19 infection to develop appropriate rehabilitation interventions to improve these symptoms.

The pathophysiology of long-term persistent symptoms is largely unknown. However, hypoxia and

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hypoxic tissue damage caused by COVID-19 associated pneumonia, decreased pulmonary diffusion capacity, ventilation-perfusion mismatch, and lung fibrosis have been hypothesized (Mittal et al., 2021). Arterial hypoxemia, which occurs due to the impact of the pulmonary system in COVID-19, may reduce the amount of oxygen transferred to the muscles, which may cause early lactate release and muscle fatigue in patients. Desaturation occurs especially during exercise in patients with post-COVID-19 syndrome. Previously it was presented that patients with more involved lungs on chest computed tomography (CT) were severely desaturated during the six-minute walk test (6-MWT) (González et al., 2021).

The literature studies investigating skeletal muscle oxygen utilization have commonly focused on healthy individuals and various disease populations (Espinosa-Ramírez et al., 2021; Louvaris et al., 2013, 2020). In hypoxemia, whole-body oxygenation is affected, and the amount of oxygen delivered to tissues is reduced, which may exacerbate peripheral fatigue (Katayama et al., 2007; Romer et al., 2007). Decreased muscle oxygenation due to rapid deoxygenation during exercise may result in muscle fatigue, triggering general fatigue. It has been shown that oxygen transport to tissues is reduced, and muscle oxygenation is impaired in chronic obstructive pulmonary disease (COPD) (Louvaris et al., 2013, 2020). In patients with COVID-19, a significant systemic inflammatory response during acute infection affects the lungs and pulmonary vessels, as well as anemia, which reduces the blood oxygen transport capacity (Baratto et al., 2021; Di Girolamo et al., 2022). In those with COPD, arterial hypoxemia may contribute to exercise intolerance by reducing the amount of oxygen delivered to locomotor muscles, leading to early lactate release and discomfort in the legs. Exercise intolerance in those with COPD may be related to decreased muscle oxygen in skeletal muscle (Maltais et al., 2014). Considering that patients with post-COVID -19 syndrome also have arterial hypoxemia, it should be investigated whether there is a decrease in oxygenation of locomotor muscles such as quadriceps femoris (QF). However the effect of hypoxemia associated with COVID-19 on oxygenation of peripheral muscles and changes during submaximal and maximal exercise intensity has not been investigated yet. In addition, being at submaximal exercise intensity (6-MWT) as a walking activity in a straight area is more representative of daily living activities than laboratory tests (cardiopulmonary exercise test (CPET)) and can better be tolerated by patients. However, maximum effort on a treadmill, such as CPET, does not well explain patients' symptoms in actual daily living activities (Balady et al., 2010; Mapelli et al., 2023). The hypothesis of this study was that QF muscle oxygen utilization during submaximal and maximal exercise tests varies and decreases more during maximal exercise in patients post-COVID-19 syndrome with pulmonary involvement. Oxygen utilization may vary depending on the muscles' increased oxygen demand during strenuous exercise. In addition, the reoxygenation response of the tissue may vary according to the intensity of the activity during the recovery phase of the muscles after exercise. Therefore, our study aimed to evaluate and compare QF muscle oxygenation during submaximal and maximal exercise tests in patients with post-COVID-19 syndrome.

Materials and methods

Patients

Thirty-nine patients with post-COVID-19 syndrome with pulmonary involvement (Centers for Disease Control and Prevention, 2023) were recruited for the study. Pulmonary involvement of the patients was determined by a pulmonologist according to CT (Lizzi et al., 2022). Patients who had at least 12 weeks after diagnosis and had long-term symptoms were included in the study. The following inclusion criteria were: patients with pulmonary involvement post-COVID-19, between the ages of 18–75 years, negative COVID-19 PCR test, and volunteer to participate in the study. Exclusion criteria were: body mass index (BMI) $\geq$35 kg/m^2, acute pulmonary exacerbation, acute upper or lower respiratory tract infection, serious neurological, neuromuscular, orthopedic diseases affecting physical functions, participation in a planned exercise program in the last three months, a cognitive impairment that causes difficulty in understanding and following exercise test instructions, contraindication for exercise testing and/or exercise training according to the American College of Sports Medicine (Thompson, Gordon, and Pescatello, 2010), cancer, renal or hepatic disease, aortic stenosis, complex arrhythmia, acute aneurysm, uncontrolled hypertension, diabetes mellitus, heart failure, and cardiovascular diseases.

Ethical approval

The study was approved by the Gazi University Ethics Committee (Protocol ID: 2022–093). Before initiation of the study, each patient was informed about the study and gave written informed consent. The study

conformed to the standards set by the Declaration of Helsinki (Harriss, Macsween, and Atkinson, 2017).

Study protocol

The patients referred from Gazi University, Faculty of Medicine, Department of Chest Diseases for pulmonary rehabilitation to Cardiopulmonary Rehabilitation Unit located in the Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, were recruited between March 2022 and June 2023.

The 6-MWT was performed to evaluate the patients' muscle oxygenation and cardiorespiratory responses during the submaximal exercise test, and CPET was performed to evaluate the responses during the maximal exercise test. The evaluations of the patients were completed in two days. Muscle oxygenation during the 6-MWT and CPET on two different days were measured and compared. The patients were evaluated by different, experienced specialist physiotherapists on the first and second days. On the first day, demographic and clinical characteristics, post-COVID-19 functional status scale (PCFS), QF muscle strength, and 6-MWT were investigated, and on the second day, CPET was performed. Activity monitor to measure physical activity was worn on each patient for five consecutive days end of the second day.

Post-COVID-19 functional status

The functional status of individuals was graded using the PCFS whose validity ($r = 0.534$, $p < .001$) and reliability (intraclass correlation coefficient (ICC): 0.734–0.880) have been established (Çalık Kütükcü et al., 2021; Klok et al., 2020). The PCFS test and retest scores have a Cronbach's alpha value of 0.821, indicating that this scale is reliable ($r = 0.707$, $p < .001$) (Çalık Kütükcü et al., 2021). According to the functional status limitation of the PCFS scale: grade 0 (no), grade 1 (negligible), grade 2 (slight), grade 3 (moderate), grade 4 (severe), and grade 5 (death) (Sacristán-Galisteo et al., 2022).

Pulmonary involvement

The chest CT images of the patients were evaluated through teleradiology for the characteristics based on Fleischner Society nomenclature recommendations (Hansell et al., 2008). Each of the five lung lobes was visually scored on a scale of 0–3 (0: no lesion, 1: <1/3 of the lobe volume involved, 2: >1/3, and < 2/3 of the lobe volume involved, 3: >2/3 of the lobe volume involved) (Chrzan et al., 2023). The total CT score for each case was the sum of the scores for the five lobes, with a maximum possible score of $5 \times 3 = 15$. A total score of ≤ 7 was considered as ≤ 50% involvement, and > 7 was considered as > 50% involvement (Yılmaz Demirci et al., 2021; Pan et al., 2020). Patients with any pulmonary involvement (≤ 50% or > 50%) were included in the study.

Pulmonary function test

Dynamic lung volumes were measured using a spirometer (Vmax 220 Sensormedics Corporation, Yorba Linda, California). Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow from 25 to 75% ($FEF_{25–75\%}$) were measured. Diffusing capacity of the lungs for carbon monoxide (DLCO), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), and RV/TLC (DLCO; Vmax 220 Sensormedics Corporation, Yorba Linda, California) were measured (Johnson and Theurer, 2014).

Physical activity level

The physical activity level of the patients was evaluated with an activity monitor (Sensewear, BodyMedia, Inc. Pittsburgh, USA). The activity monitor was worn on the triceps brachii muscle of the patient's non-dominant arm for five consecutive days/week. Average metabolic equivalents (METs/day) and the number of steps (steps/day) were measured via an activity monitor (Watz, Waschki, Meyer, and Magnussen, 2008), and averages of all data were analyzed "BodyMedia® SenseWear® 7.0 Software" program. Physical activity level was categorized into METs values and number of steps (Ainsworth et al., 2011; Tudor-Locke and Bassett, 2004).

Cardiopulmonary exercise test

The maximal exercise capacity was evaluated with CPET. The test was performed using the CareFusion (Oxycon mobile version 02.00, Berlin, Germany) device via the breath-by-breath method while on a treadmill (Trackmaster, 3017 Full Vision, Georgia, USA). Electrocardiography evaluation was performed with the 12-lead electrocardiography CareFusion Version 02.00 electrocardiography system (Pulse Biomedical, Inc., 935 S, Pennsylvania, USA). Participants were asked to avoid physical activities for 24 hours before CPET and to avoid alcohol, caffeine, and other stimulants and food for at least 8 hours before the evaluations. All calibrations of the device were performed before the test. Resting data were recorded for 3 minutes before

testing. The first three minutes of the CPET consisted of a warm-up period, then a loading period, and the last three minutes of a recovery period.

The test was performed using a ramp protocol consisting of gradual increases in speed and incline for a total exercise time of approximately 8–12 minutes. The workload was increased every minute by increasing both the speed and inclination of the load. It was determined that the patient reached maximal exercise capacity according to heart rate (HR), heart rate reserve (HRR), and respiratory exchange rate (RER) values. The peripheral oxygen saturation (SpO_2) of the patients while resting and during the test and recovery were measured with an earlobe probe connected to the Oxycon mobile system. According to the criteria of the American Thoracic Society (ATS) and the American Academy of Chest Physicians the test was terminated when there was a symptom (such as dyspnea, fatigue, chest pain, dizziness, claudication) that would prevent the continuation of the test (American Thoracic Society and American College of Chest Physicians, 2003). When the patients reached maximum HR (HRR <10, peak HR > 90% predicted), RER exceeded 1.1, or had severe symptoms (dyspnea, chest pain, fatigue), the test was terminated, and a recovery period was started. Chronotropic incompetence in CPET was defined as the inability of the individual to reach 80% of the peak HR that should be achieved according to age. Chronotropic index: ((Peak HR-resting HR)/((220-age)-resting HR))*100 was calculated (Lauer et al., 1999). The maximal HR of patients using beta blockers was calculated as 119+(resting HR/2)-(age/2). The abnormal response was defined as chronotropic incompetence < 80% (Cole et al., 1999).

Six-minute walk test

Submaximal exercise capacity was evaluated with the 6-MWT, whose reliability has been established in idiopathic pulmonary fibrosis (Holland et al., 2018). The test was performed in accordance with ATS guidelines (American Thoracic Society, 2002; Holland et al., 2014). The reliability of the 6-MWT is very high (ICC: 0.96). Patients were asked to walk as fast as possible within 6 minutes in a closed, quiet corridor 30 m long. Standard expressions were used, and the patient was told how much time was left until the end of the test every 60 seconds. The patient was stopped and rested during the test for symptoms such as dyspnea, chest pain, and dizziness. Patients were encouraged to continue testing with standard expressions every 30 seconds while they paused and rested. Heart rate (Polar FT I00, China), systolic blood pressure (SBP), diastolic blood pressure (DBP), breathing frequency (BF), SpO_2 (Model 9590 Oximeter Nonin Medical, Inc, Plymouth, MN, USA), dyspnea, fatigue, and leg fatigue were questioned before, and after the test (Modified Borg Scale) and at 1st minutes of recovery. The SpO_2 was measured using a finger-type pulse oximetry probe. The test was repeated twice on the same day, with a minimum interval of 30 minutes between tests. For the analysis, the longest distance presented between the two tests was used (American Thoracic Society, 2002). The percent of the predicted value of 6-MWT length was calculated with the reference equation of Gibbons et al (Gibbons, Fruchter, Sloan, and Levy, 2001). Fall in SpO_2 ≥4 was described as desaturation.

Muscle oxygenation

The muscle oxygen saturation (SmO_2) was evaluated using the Moxy® device (Moxy®, Fortiori Design LLC, Minnesota, USA), which is a valid and reliable noninvasive method (Crum et al., 2017). The Moxy® device is a small near-infrared spectroscopy (NIRS) system. Moxy is a device that measures the muscles' local oxygen saturation and total hemoglobin in the muscle capillaries below the motor point of the muscle. The Moxy device uses four wavelengths of NIRS light at 630–850 nm and the sensor includes a single light emitting diode and two detectors positioned 12.5 and 25.0 mm from the source. The emitted light is processed by an algorithm that uses the tissue light propagation model and the Beer-Lambert law to determine the amount of light absorbed at the wavelengths of oxygenated and deoxygenated hemoglobin. This calculates the percentage of hemoglobin containing oxygen as well as total hemoglobin (THb) present under the tissue in which the device is placed. Since light passing through microvessels larger than 1 mm in diameter is expected to be completely absorbed, the majority of reflected light is assumed to come from capillaries, and therefore the resulting measurements reflect muscle oxygenation (Crum et al., 2017; Fortiori Design LLC, 2015). Quadriceps femoris muscle oxygen and THb level were measured before the CPET and the 6-MWTs at rest, during, and after the test in first-minute recovery. The Moxy® device was placed on the 1/3 lower motor point of the QF muscle with an anti-allergic plaster. Resting measurements were taken at 3 minutes after the device was placed. Minimum SmO_2 ($SmO_{2\,min}$), and maximum SmO_2 (SmO_{2max}), minimum THb (THb_{min}), and maximum THb (THb_{max}) values were measured. The SmO_2 values were recorded as percent (%) and THb values in g/dl. Moxy oxygen monitor is a valid and reliable method for measuring

muscle oxygenation. There is a strong or very large correlation for SmO_2 with Spearman's Order-Rank coefficient (0.834–0.980) and ICC (0.773–0.992). For THb, there is a strong reliability of the coefficient of variation of ≤ 1% between tests for all exercise intensities (Crum et al., 2017).

Peripheral muscle strength

The QF isometric muscle strength was evaluated using a hand-held dynamometer (JTECH Power Track Commander, Baltimore, MA, USA). The measurement was performed while the patient was in a sitting position, with the hips and knees flexed at 90 degrees and the hands on the chest. The QF was tested three times, and the highest value was recorded. The percent of the predicted value QF strength was calculated with the reference equation Andrews et al (Andrews, Thomas, and Bohannon, 1996).

Statistical analysis

Statistical analyses were performed using the SPSS 26.0 statistical package (SPSS, Chicago, IL, USA). Normality was evaluated with the Shapiro–Wilk test. According to normal and non-normal distributions, descriptive statistics were expressed as mean±standard deviation and median (interquartile range). Chi-square tests examined categorical variables. Paired Student's *t*-test (for normal distributed data) and Wilcoxon test (for non-normal distributed data) were used to compare the responses and muscle oxygenation measurements between the two exercise tests. Power analysis was calculated using THb_{max} values. Statistical significance was set at $p < .05$.

Results

Fifty-three patients with pulmonary involvement post-COVID-19 syndrome were included in the study, and thirty-nine patients were analyzed (Figure 1). Demographics and clinical data of age, height, weight, BMI, durations of hospitalization, intensive care unit, mechanical ventilation, corticosteroids, and PCFS, average METs (METs/day), number of steps (steps/day), QF muscle strength are shown in Table 1. The majority of our patients had mild (38.5%) and moderate (48.7%) functional limitations, according to PCFS. None of the patients participated in a planned exercise program for

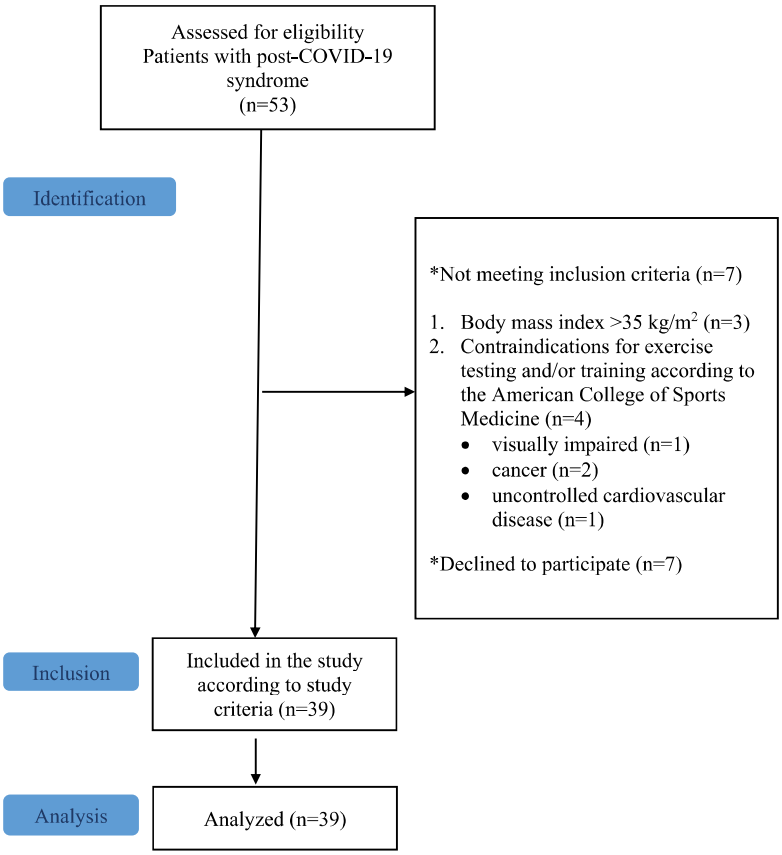

Figure 1. The flow diagram of the patients with the post-coronavirus disease 2019 syndrome.

Table 1. Demographic, pulmonary, physical activity, and exercise capacity values in patients with post-coronavirus disease 2019 syndrome.

	Mean ± SD/Median ($IQR_{25–75\%}$)
Female/Male (n/%)	18 (46.2%)/21 (53.8%)
Age (years)	61.0 (54–67)
Height (cm)	165.35 ± 9.59
Weight (kg)	76.63 ± 13.77
Body mass index (kg/m^2)	27.99 ± 4.26
• Cachexia (<18.5 kg/m^2)	0 (0%)
• Normal (18.6–24.9 kg/m^2)	11 (28.2%)
• Overweight (25.0–29.9 kg/m^2)	13 (33.3%)
• Class I Obese (30.0–34.9 kg/m^2)	15 (38.5%)
FEV_1 (%)	87.97 ± 22.44
FVC (%)	97 (77–108.5)
FEV_1/FVC	78.53 (72.01–83.4)
PEF (%)	87.4 ± 22.06
$FEF_{25–75\%}$ (%)	65.62 ± 28.37
DLCO (%)	75.5 ± 21.92
TLC (%)	76.42 ± 20.40
FRC (%)	80.40 ± 21.77
RV (%)	84.57 ± 22.91
RV/TLC (%)	54.72 ± 32.00
Lung infiltrates on CT	
≤50%	29 (74.3%)
>50%	10 (25.7%)
Comorbidity (n/%)	36 (92.3%)
Hypertension	17 (43.6%)
Coronary Artery Disease	11 (28.2%)
Diabetes Mellitus	6 (15.4%)
Asthma	5 (12.8%)
COPD	4 (10.2%)
Heart Failure	3 (7.7%)
ILD	3 (7.7%)
Scoliosis	2 (5.1%)
Psoriasis	2 (5.1%)
Cancer	2 (5.1%)
Charlson comorbidity index score (0–37 points)	0 (0–1)
Very light (0) (n/%)	21 (53.8%)
Light (1–2) (n/%)	16 (41.1%)
Heavy (3–4) (n/%)	2 (5.1%)
Very heavy (≥5) (n/%)	0 (0%)
Hospitalization (n/%)	24/61.5%
Duration of hospitalization (day)	15.75 ± 9.70
Intensive care unit (n/%)	11/28.2%
Duration of intensive care unit (day)	8.00 ± 9.70
Mechanically ventilation (n/%)	7/17.9%
Duration of mechanical ventilation (day)	6.50 ± 9.70
Corticosteroid use (n/%)	20/51.3%
Duration of corticosteroid use (day)	22.25 ± 26.10
Corticosteroids dose (mg)	11.25 ± 9.5
Time from COVID-19 diagnosis (weeks)	81.28 ± 35.51
PCFS (0–4 points)	2 (2–3)
PCFS 0	2 (5.1%)
PCFS 1	3 (7.7%)
PCFS 2	15 (38.5%)
PCFS 3	19 (48.7%)
PCFS 4	0 (0%)
Average METs (METs/day)	1.30 (1.20–1.40)
According to average METs	
• Inactive (n/%)	34 (87.2%)
• Low active (n/%)	5 (12.8%)
Number of steps (steps/day)	5678.94 ± 3331.62
According to the number of steps	
• Inactive (n/%)	19 (48.7%)
• Low active (n/%)	8 (20.5%)
• Somewhat active (n/%)	7 (17.9%)
• Active (n/%)	4 (10.3%)
• Highly active (n/%)	1 (2.6%)
QF strength (N) (ND)	234.82 ± 48.86
QF strength (%) (ND)	67.82 ± 14.77
QF strength (N) (D)	232.71 ± 47.24
QF strength (%) (D)	65.24 ± 18.45
6-MWT (m)	490.5 (425.5–559.2)
6-MWT (%)	72.26 ± 14.27

Table 2. Cardiopulmonary exercise test results in patients with post-coronavirus disease 2019 syndrome.

Peak exercise	Mean ± SD
RER	1.03 ± 0.15
MET	5.17 ± 1.37
VO_{2peak} (ml/min)	1412.92 ± 440.39
VO_{2kg} (ml/min/kg)	18.15 ± 4.75
VO_{2peak} (%)	80.82 ± 20.83
VCO_{2peak} (ml/min)	1469.89 ± 534.66
VE_{peak} (l/min)	65.64 ± 19.43
HR (beats/min)	146.98 ± 18.00
HR (%)	94.66 ± 8.10
HRR (beats/min)	9.26 ± 12.49
VO_2/HR (ml/beats)	9.58 ± 2.77
VO_2/HR (%)	83.23 ± 25.53
BF (breaths/min)	37.94 ± 12.49
SpO_2 (%)	91.76 ± 7.99
EqO_2	43.62 ± 9.50
$EqCO_2$	42.59 ± 7.69
BR (%)	30.82 ± 6.38

RER: Respiratory exchange ratio, MET: Metabolic equivalent, VO_{2peak}: peak oxygen uptake, VCO_{2peak}: peak carbon dioxide output, VE_{peak}: peak minute ventilation, BF: Breathing frequency, HR: Heart rate, HRR: Heart rate reserve, VO_2/HR: Oxygen pulse, SpO_2: Peripheral oxygen saturation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, EqO_2: Ventilatory equivalent of oxygen, $EqCO_2$: Ventilatory equivalent of carbon dioxide, BR: Breathing reserve, SD: Standard deviation, ml: milliliter, min: minutes, kg: kilogram, l: liter, %: percentage.

the last three months. Various comorbidities were present in 19 (48.7%) patients and BMI ≥30 kg/m^2 in 15 (38.4%) patients. The 34 (87.2%) and 19 (48.7%) patients did not meet the average METs and number of steps, respectively. Seven (17.9%) patients had a restrictive type, and 8 (20.5%) patients had obstructive; 7 (17.9%) patients had mixed type pulmonary function abnormalities, and 15 (38.4%) of patients TLC, 18 (46.1%) of DLCO were decreased. Dominant and non-dominant QF muscle strength was less than 80% of predicted in 29 (74.4%) and 30 (76.9%) patients, respectively (Table 1).

Twenty-three (58.9%) patients walked less than 80% of the predicted 6-MWT distance. Five (12.8%) of the patients reached maximal HR during 6-MWT. Cardiopulmonary exercise test results in patients are shown in Table 2. Percent predicted VO_{2peak} was <80% in 20 (51.3%) patients. Three (7.7%) patients could not reach maximal HR during CPET; the tests were terminated due to patients' severe dyspnea and fatigue perception. The median chronotropic index of the patients in CPET was 93% (86–100), and the chronotropic index response of 7 (17.9%) patients was abnormal. Desaturation was observed in 22 (56.4%) patients during 6-MWT and 16 (41%) patients during CPET. In CPET, 28 (71.8%) of patients reached maximal HR and completed the test, 9 (23.1%) of the patients terminated the test because of dyspnea, 1 (2.6%) of fatigue, and 1 (2.6%) of chest pain.

Before-test, end-of-test, and recovery phase values for HR, SpO_2, SBP, DBP, BF, dyspnea, fatigue, and leg fatigue scores for both exercise tests are shown in Table 3. There were no significant differences in resting HR, SBP, DBP, BF, dyspnea, fatigue, and leg fatigue between the 6-MWT and CPET ($p > .05$). The SpO_2 resting was higher in CPET than 6-MWT, possibly due to the measurement technique ($p < .001$). End-of-test maximal and percent predicted HR; end-of-test, recovery, and difference between post and pre test (Δ) values of HR, SBP, BF, dyspnea, fatigue, and leg fatigue; end-of -test, and Δ DBP were significantly increased in CPET than in 6-MWT ($p < .05$). The QF muscle oxygenation results of the patients during 6-MWT and CPET are given in Table 4. The SmO_{2min}, $SmO_{2recovery}$, and $SmO_{2recovery\text{-}avarage}$ are significantly decreased, and Δ SmO_2 and THb_{max} were significantly more during CPET than 6-MWT (1-β = 0.66, $p < .05$).

Discussion

This study found that post-COVID-19 patients with pulmonary involvement had lower skeletal muscle oxygen saturation at the microcirculatory level than submaximal during maximal exercise testing, which may contribute to exercise intolerance. Since near-infrared reflectance spectroscopy measurements provide a dynamic assessment of muscle oxygen (Ferrari, Mottola, and Quaresima, 2004), muscle oxygen saturation recovery was better at submaximal exercise intensities. In addition, total hemoglobin was found to be higher during CPET compared to 6-MWT. This may be related to an increase in the amount of total hemoglobin due to a proportional increase in blood flow velocity in the upstream and downstream vessel blood (Laughlin et al., 2012) to increase oxygen delivery to the muscles during maximal exercise. To our knowledge, this is the first study to compare muscle oxygen saturation and total hemoglobin in skeletal muscle during submaximal and maximal exercise.

Decreased muscle oxygen saturation may be due to the two different physiological changes. First, capillary flow disturbances after COVID-19 infection limit oxygen transport in the lungs and tissues and can, therefore, cause hypoxemia and tissue hypoxia (Østergaard, 2021).

cm: centimeter, kg: kilogram, kg/m^2: kilogram/meter square, n: frequency, %: percentage, m: meter, PCFS: Post COVID-19 functional status scale, MET: Metabolic equivalent, mg: milligram, FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, $FEF_{25-75\%}$: Forced expiratory flow from 25 to 75%, DLCO: Pulmonary diffusion capacity, TLC: Total lung capacity, FRC: Functional residual capacity, RV: Residual volume, QF: Quadriceps femoris, 6-MWT: Six-minute walk test, CT: Computed tomography, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease, ND: non-dominant, D: dominant, N: Newton, IQR: Interquartile range, SD: Standard deviation

Table 3. Comparison of cardiorespiratory parameters during six-minute walk test and cardiopulmonary exercise test in patients with post-coronavirus disease 2019 syndrome.

	6-MWT	CPET	
	Mean ± SD Median ($IQR_{25–75\%}$)	Mean ± SD Median ($IQR_{25–75\%}$)	p
HR (beats/min)			
Resting	80.46 ± 12.21	85.69 ± 14.92	0.095
End	122 (111–135)	151 (138–163)	**< 0.001***
Recovery	96 (87–107)	135 (123–143)	**< 0.001***
ΔHR	42 (28–55)	65 (49–78)	**< 0.001***
HR (%)	78 (73–86)	96.5 (93–100)	**< 0.001***
SpO_2 (%)			
Resting	96 (93–97)	99 (98–99)	**< 0.001***
End	93 (88–95)	95 (90–98)	0.079
Recovery	96 (93–97)	97 (90–99)	0.365
Δ SpO_2	4 (1–6)	4 (1–8)	0.244
SBP (mmHg)			
Resting	120 (110–130)	120 (110–120)	0.925
End	140 (130–140)	150 (140–160)	**0.005***
Recovery	130 (120–135)	140 (130–150)	**0.007***
Δ SBP	20 (10–30)	30 (20–40)	**0.013***
DBP (mmHg)			
Resting	70 (70–90)	80 (80–80)	0.072
End	80 (80–90)	90 (90–90)	**0.001***
Recovery	80 (70–90)	80 (80–90)	0.060
Δ DBP	10 (0–10)	10 (10–10)	**0.023***
BF (breath/min)			
Resting	20 (20–24)	21 (18–24)	0.239
End	32 (28–32)	41 (35–47)	**< 0.001***
Recovery	24 (20–28)	32 (30–38)	**< 0.001***
Δ BF	12 (8–12)	19 (14–25)	**< 0.001***
Dyspnea (M. Borg Scale 0–10 points)			
Resting	0 (0–0)	0 (0–0)	0.519
End	2 (0–3)	3 (3–5)	**< 0.001***
Recovery	0 (0–2)	2 (1–3)	**0.001***
Δ Dyspnea	2 (0–3)	3 (2–5)	**< 0.001***
Fatigue (M. Borg Scale 0–10 points)			
Resting	0 (0–0)	0 (0–0)	0.698
End	2 (0–3)	3 (1–4)	**0.028***
Recovery	0 (0–2)	2 (0–3)	**0.026***
Δ Fatigue	2 (0–3)	2 (1–4)	**0.047***
Leg fatigue (M. Borg Scale 0–10 points)			
Resting	0 (0–0)	0 (0–0)	0.979
End	0 (0–2)	3 (1–4)	**< 0.001***
Recovery	0 (0–2)	2 (0–3)	**0.003***
Δ Leg Fatigue	0 (0–2)	3 (1–4)	**< 0.001***

M. Borg Scale: Modified Borg scale, 6-MWT: Six-minute walk test, CPET: Cardiopulmonary exercise test, HR: Heart rate, SpO_2: Peripheral oxygen saturation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, mmHg: Millimeters of mercury, BF: Breathing frequency, min: minutes, Δ: Difference between post and pre test value, SD: Standard deviation, *$p < .05$.

Second, the decrease in mitochondria function (Saleh, Peyssonnaux, Singh, and Edeas, 2020) in the muscles may impair muscle oxygen transport and reduce muscle oxygenation. In COVID-19 patients, systemic inflammatory response during acute infection affects the lungs and pulmonary vessels and muscle mitochondria function, as well as anemia, which reduces the oxygen-carrying capacity of the blood (Baratto et al., 2021; Di Girolamo et al., 2022; Shang et al., 2022). Shang et al. (2022) reported found that the SARS-CoV-2 virus damaged mitochondrial function (Shang et al., 2022). In our study, the deterioration in mitochondrial function after COVID-19 may, have affected muscle oxygenation (Shang et al., 2022). Muscle oxygenation decreased during both the maximal and submaximal exercise tests; however, the difference in maximum-minimum muscle oxygenation during the test was more significant in the maximal exercise. Due to muscle deoxygenation trends during high-intensity exercise (Bhambhani, 2004), increased workload (incline and speed) in CPET may have increased the oxygen uptake of the muscles. In the present study, the HR recovery response was better after the maximal exercise than the submaximal test, while the muscle saturation recovery

Table 4. Comparison of muscle oxygenation during six-minute walk test and cardiopulmonary exercise test in patients with post-coronavirus disease 2019 syndrome.

	6-MWT	CPET		
	Mean ± SD Median ($IQR_{25–75\%}$)	Mean ± SD Median ($IQR_{25–75\%}$)	Mean difference 95% CI	p
$SmO_{2resting}$ (%)	51.48 ± 16.63	47.39 ± 16.82	4.09 (–3.5 to 11.68)	0.287
$SmO_{2maximum}$ (%)	51.12 ± 19.15	50.81 ± 19.39	0.31 (8.43 to 9.06)	0.943
$SmO_{2minimum}$ (%)	28.74 ± 17.54	21.47 ± 14.18	7.26 (0.17 to 14.52)	0.049*
ΔSmO_2 (%)	20 (13–30)	25 (17–36)	–	0.043*
$SmO_{2avarage\text{-}min}$ (%)	29.71 ± 17.48	23.26 ± 14.29	6.45 (–0.80 to 13.71)	0.081
$SmO_{2avarage\text{-}max}$ (%)	51.61 ± 19.0	50.76 ± 19.34	0.85 (–7.85 to 9.55)	0.846
$SmO_{2recovery}$ (%)	46.92 ± 18.01	37.39 ± 17.35	8.86 (0.79 to 16.93)	0.021*
$SmO_{2recovery\text{-}average}$ (%)	46.15 ± 18.29	36.52 ± 17.83	9.52 (1.49 to 17.55)	0.014*
$THb_{resting}$ (g/dl)	12.29 ± 0.41	12.32 ± 0.40	–0.02 (–0.21 to 0.16)	0.829
$THb_{maximum}$ (g/dl)	12.24 ± 0.35	12.42 ± 0.31	–0.19 (–0.34 to –0.36)	0.012*
$THb_{minimum}$ (g/dl)	11.83 ± 0.37	11.91 ± 0.49	–0.94 (–0.29 to 0.10)	0.341
ΔTHb (g/dl)	0.35 (0.22–0.49)	0.49 (0.26–0.75)	–	0.065
$THb_{recovery}$ (g/dl)	12.13 ± 0.43	12.22 ± 0.45	–0.10 (0.31 to –0.10)	0.314

6-MWT: Six-minute walk test, CPET: Cardiopulmonary exercise test, SmO_2: Muscle oxygen saturation, THb: Total hemoglobin, %: percentage, min: minimum, max: maximum, g: gram, dl: deciliter, Δ: Difference between post and pretest value, SD: Standard deviation, IQR: Interquartile range, CI: Confidence interval, *$p < .05$.

response was worse. This situation may show that cardiac system responses are good and peripheral oxygen extraction responses are poor in recovery after exercise in patients with post-COVID-19 syndrome. In addition, it was determined that the total hemoglobin levels of the patients increased more during maximal exercise compared to submaximal exercise. In the case of systemic capillary hypoxia, the body increases the number of blood cells by secreting erythropoietin with vasodilation in the circulatory system, and therefore, the amount of hemoglobin in the blood increases (Hida et al., 2002). Considering that the oxygen requirement used by the muscle during maximal exercise is increased compared to submaximal exercise, the total hemoglobin amount may be increased in maximal exercise depending on the increased blood flow. Due to the increase in respiratory expenditure during exercise, there is more blood flow to the respiratory muscles and, possibly restricting the oxygen supply to the locomotor muscles, which is called metaboreflex (Boushel, 2010). During CPET, the QF muscle may have less oxygen due to the increased breathing work at maximal workload. In order to better reveal the effect of the metaboreflex in these patients, oxygenation of both locomotor and intercostal muscles separately during submaximal and maximal exercise should be investigated in future studies.

Our study found that oxygen consumption decreased in 51% of patients with post-COVID-19 syndrome with pulmonary involvement. Clavario et al. (2021) found that half of patients had reduced oxygen consumption in their COVID-19 patients at three months follow-up (Clavario et al., 2021). Barbagelata et al. (2022) found that about one-third of post-COVID-19 patients had reduced oxygen consumption, and Singh et al. (2022) found that oxygen consumption of patients who recovered from COVID-19 decreased compared to healthy controls (Barbagelata et al., 2022; Singh et al., 2022). Our results are in agreement with those in the literature. Peak oxygen consumption is an important parameter that indicates the capacity of the pulmonary, cardiovascular, and muscular systems to uptake, transport, and utilize oxygen (Poole, Wilkerson, and Jones, 2008). Patients' impaired oxygen consumption may be due to intrapulmonary or extrapulmonary reasons. The leading intrapulmonary causes are pulmonary dysfunction and gas exchange abnormalities. Post-COVID-19 syndrome patients exhibit abnormalities in lung function that may be due to pathological lung changes caused by the SARS-CoV-2 virus (Torres-Castro et al., 2021). The present study found that approximately half of the patients (46%) had impaired pulmonary diffusion capacity. In the literature, it has been determined that the pulmonary diffusion capacity of the patients decreases due to the damage in the pulmonary vascular structures after COVID-19 and that the decrease in exercise capacity may be related to this impairment (Chen et al., 2020; Huang et al., 2020; Mo et al., 2020). Intrapulmonary involvement may explain the decrease in oxygen consumption in these patients.

SARS-CoV-2 virus may cause myalgia, muscle weakness, and fatigue in the neuromuscular system due to inflammation in the acute phase of the disease (Hasan et al., 2021). Inflammatory cytokines and dysregulated host response directly affect immune cells, causing muscle atrophy and musculoskeletal problems (Soares et al., 2022). In this study, the QF muscle strength of the patients was decreased. Clavario et al. (2021) found that in COVID-19 patients, there is an

independent relationship between dominant leg extension maximum strength and peak oxygen consumption, and this may be associated with bed rest and subsequently muscular deconditioning, but also with a potential role for corticosteroid myopathy (Clavario et al., 2021). Peripheral muscle weakness, an extrapulmonary cause, may also explain the impaired oxygen consumption.

Many elements of human physiology respond to environmental changes throughout the day. Physiological responses of the cardiorespiratory system, such as changes in HR and BF, may be impaired by acute hypoxia (Bosco et al., 2003), a common symptom of severe COVID-19. Omar, Ferreira, Hegazy, and Alaparthi (2023) examined cardiorespiratory response during 6-MWT in patients with COVID-19 and found that patients had higher HR and BR than healthy controls (Omar, Ferreira, Hegazy, and Alaparthi, 2023). Milani et al. (2023) found that patients with severe disease had lower peak HR than controls and those with mild disease. In addition, it was found that peak HR decreased after COVID-19 infection compared to pre-infection in moderate/severe patients (Milani et al., 2023). In our study, most patients achieved peak HR during maximum exercise, and normal HR response was observed during submaximal exercise. End-of-test HR was significantly elevated in both tests, and the increase was more remarkable in the maximal exercise test than in the submaximal exercise test. In future studies, comparing post-COVID-19 patients and healthy controls during submaximal and maximal exercises provides more detailed information about how the cardiorespiratory responses change during exercise intensity.

Longobardi et al. (2022) found that COVID-19 survivors presented with blunted chronotropic responses (chronotropic index, maximum HR, and HR recovery) and presented that patients had more chronotropic insufficiency than healthy controls (Longobardi et al., 2022). In our study, the majority of patients had good chronotropic responses. To our knowledge, available evidence suggests that cardiac output is maintained. Still, peripheral oxygen extraction is decreased in survivors of COVID-19 (Baratto et al., 2021; Singh et al., 2022), suggesting an impairment in oxidative metabolism resulting from this disease. While the chronotropic responses of our patients are as expected, it may be inferred that decreased oxygen consumption and abnormal responses in muscle oxygenation may be related to the defect in oxidative metabolism.

In our study, SpO_2 measured with the earlobe probe recorded higher measurement results than the finger probe. This may be related to measuring saturation from the finger during 6-MWT and the earlobe probe that is, centrally, during CPET. In the study by Seifi et al. (2018) it was determined that the earlobe probe had a higher compliance rate with SpO_2 measured in arterial blood gas analysis compared to finger and other probe types (Seifi et al., 2018). The literature found that patients who had COVID-19 were desaturated at the end of the submaximal and maximal exercise tests (Cortés-Telles et al., 2021; Paneroni et al., 2021). In the study, patients had desaturation during both 6-MWT and CPET. Our patients had lung involvement, and desaturation was observed at both exercise intensities due to pulmonary gas exchange abnormalities during exercise. In addition, this study found that patients experienced more general and leg fatigue in maximal exercise than in submaximal exercise. De Boer et al. (2022) reported lower rates of fat β-oxidation and increased blood lactate (an acidic end product of anaerobic metabolism) levels during exercise in patients with acute sequelae whose main symptoms are fatigue and exercise dyspnea (De Boer et al., 2022). A higher perception of fatigue may have occurred during maximal exercise because anaerobic metabolism energy sources are used longer.

Limitations and future directions

Due to the increase in vaccination and decrease in the severity of virus variants, controlling the COVID-19 pandemic limited including more of patients in this study, recently. In addition, if the responses to muscle oxygenation in submaximal and maximal exercise tests were compared with healthy controls in this study, it could better reveal the muscle oxygen impairment in patients with post-COVID-19 syndrome. The power of the present study is 66%, calculated using THb_{max} values. Hence, more than the sample size may be needed to detect differences for some parameters.

Conclusion

The main findings of this study were that post-COVID-19 patients with lung involvement have lower skeletal muscle oxygen saturation and higher total hemoglobin and physiological responses of the cardiorespiratory system during maximal exercise compared to submaximal exercise. Decreased muscle oxygen saturation may be associated with pulmonary and peripheral muscle impairment. In particular, in post-COVID-19 syndrome patients with pulmonary involvement, measuring peripheral oxygen saturation with a pulse oximeter does not accurately detect hypoxia. Therefore, muscle deoxygenation and the effects of a variety of exercise training on the muscle oxygen

responses of the patients should be evaluated during exercise. One of the strengths of this study is that maximal exercise capacity was evaluated with a CPET, a gold-standard method. Post-COVID-19 is a syndrome with various disease severity, from asymptomatic to severe. Including patients with lung involvement by CT in our study was another strength of our research.

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Authors' contributions

Guarantor statement: corresponding author BKK, study director MBG, and authors BKK, MBG, EB, and NYD are responsible for all manuscript content, including the data and analysis, and declare the study is original research. Author contributions: All authors had full access to all of the data in the study. MBG: conception and design; BKK, EB, NYD data acquisition; BKK, MBG data analysis data interpretation; BKK, MBG, EB, NYD manuscript draft, critical revision, and final approval.

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References

Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS 2011 Compendium of physical activities: a second update of codes and MET values. Medicine & Science in Sports & Exercise 43: 1575–1581.

American Thoracic Society; American College of Chest Physicians 2003 ATS/ACCP statement on cardiopulmonary exercise testing. American Journal of Respiratory and Critical Care Medicine 167: 211–277.

Andrews AW, Thomas MW, Bohannon RW 1996 Normative values for isometric muscle force measurements obtained with hand-held dynamometers. Physical Therapy 76: 248–259.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002 ATS statement: Guidelines for the six-minute walk test American Journal of Respiratory and Critical Care Medicine 166: 111–117.

Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, et al. 2010 Clinician's Guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 122: 191–225.

Baratto C, Caravita S, Faini A, Perego GB, Senni M, Badano LP, Parati G 2021 Impact of COVID-19 on exercise pathophysiology: A combined cardiopulmonary and echocardiographic exercise study. Journal of Applied Physiology 130: 1470–1478.

Barbagelata L, Masson W, Iglesias D, Lillo E, Migone JF, Orazi ML, Maritano Furcada J 2022 Cardiopulmonary exercise testing in patients with post-COVID-19 syndrome. Medicina Clinica 159: 6–11.

Bhambhani YN 2004 Muscle oxygenation trends during dynamic exercise measured by near-infrared spectroscopy. Canadian Journal of Applied Physiology 29: 504–523.

Bosco G, Ionadi A, Panico S, Faralli F, Gagliardi R, Data P, Mortola JP 2003 Effects of hypoxia on the circadian patterns in men. High Altitude Medicine & Biology 4: 305–318.

Boushel R 2010 Muscle metaboreflex control of the circulation during exercise. Acta Physiologica 199: 367–383.

Çalık Kütükcü E, Cakmak A, Kınacı E, Uyaroglu OA, Vardar Yaglı N, Sain Güven G, Sağlam M, Özışık L, Çalık Başaran N, İnal İnce D 2021 Reliability and validity of the Turkish version of post-COVID-19 functional status scale. Turkish Journal of Medical Science 5: 2304–2310.

Centers for Disease Control and Prevention 2023 Post-COVID conditions: Information for healthcare providers.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html. Accessed January 2024.
Chen R, Gao Y, Chen M, Jian W, Lei C, Zheng J, Li S 2020 Impaired pulmonary function in discharged patients with COVID-19: More work ahead. European Respiratory Journal 56: 2002194.
Chrzan R, Wizner B, Sydor W, Wojciechowska W, Popiela T, Bociąga-Jasik M, Olszanecka A, Strach M 2023 Artificial intelligence guided HRCT assessment predicts the severity of COVID-19 pneumonia based on clinical parameters. BMC Infectious Diseases 23: 314.
Clavario P, De Marzo V, Lotti R, Barbara C, Porcile A, Russo C, Beccaria F, Bonavia M, Bottaro LC, Caltabellotta M et al. 2021 Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. International Journal of Cardiology 340: 113–118.
Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS 1999 Heart rate recovery immediately after exercise as a predictor of mortality. The New England Journal of Medicine 341: 1351–1357.
Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, Pou-Aguilar YN, Wong AW, Milne KM, Ryerson CJ, Guenette JA 2021 Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. Respiratory Physiology & Neurobiology 288: 103644.
Crum EM, O'Connor WJ, Van Loo L, Valckx M, Stannard SR 2017 Validity and reliability of the moxy oxygen monitor during incremental cycling exercise. European Journal of Sport Science 17: 1037–1043.
De Boer E, Petrache I, Goldstein NM, Olin JT, Keith RC, Modena B, Mohning MP, Yunt ZX, San-Millán I, Swigris JJ 2022 Decreased fatty acid oxidation and altered lactate production during exercise in patients with post-acute COVID-19 syndrome. American Journal of Respiratory and Critical Care Medicine 205: 126–129.
Di Girolamo FG, Fiotti N, Sisto UG, Nunnari A, Colla S, Mearelli F, Vinci P, Schincariol P, Biolo G 2022 Skeletal muscle in hypoxia and inflammation: Insights on the COVID-19 pandemic. Frontiers in Nutrition 22: 865402.
Espinosa-Ramírez M, Moya-Gallardo E, Araya-Román F, Riquelme-Sánchez S, Rodriguez-García G, Reid WD, Viscor G, Araneda OF, Gabrielli L, Contreras-Briceño F 2021 Sex-differences in the oxygenation levels of intercostal and vastus lateralis muscles during incremental exercise. Frontiers in Physiology 12: 738063.
Fernández-de-Las- Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, Navarro-Santana M 2021 Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. European Journal of Internal Medicine 92: 55–70.
Ferrari M, Mottola L, Quaresima V 2004 Principles, techniques, and limitations of near-infrared spectroscopy. Canadian Journal of Applied Physiology 29: 463–487.
Fortiori Design LLC 2015 Introduction to muscle oxygen monitoring with Moxy. http://cdn2.hubspot.net/hub/188620/file-433442739-pdf/docs/moxy-ebook-intro-to-muscleoxygen.pdf?t=1488816603832. Accessed January 2024.
Gibbons WJ, Fruchter N, Sloan S, Levy RD 2001 Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. Journal of Cardiopulmonary Rehabilitation 21: 87–93.
González J, Benítez ID, Carmona P, Santisteve S, Monge A, Moncusí-Moix A, Gort-Paniello C, Pinilla L, Carratalá A, Zuil M, et al. 2021 Pulmonary function and radiologic features in survivors of critical COVID-19: A 3-month prospective cohort. Chest 160: 187–198.
Hansell DM, Bankier AA, MacMahon H, TC M, Müller NL, Remy J 2008 Fleischner Society: Glossary of terms for thoracic imaging. Radiology 246: 697–722.
Harriss D, Macsween A, Atkinson G 2017 Standards for ethics in sport and exercise science research: 2018 update. International Journal of Sports Medicine 38: 1126–1131.
Hasan LK, Deadwiler B, Haratian A, Bolia IK, Weber AE 2021 Petrigliano FA 2021 effects of COVID-19 on the musculoskeletal system: Clinician's guide. Orthopedic Research and Reviews 21: 141–150.
Hida W, Tun Y, Kikuchi Y, Okabe S, Shirato K 2002 Pulmonary hypertension in patients with chronic obstructive pulmonary disease: Recent advances in pathophysiology and management. Respirology 7: 3–13.
Holland AE, Hill CJ, Dowman L, Glaspole I, Goh N, Lee AL, CF M 2018 Short- and long-term reliability of the 6-minute walk test in people with idiopathic pulmonary fibrosis. Respiratory Care 63: 994–1001.
Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F et al. 2014 An official European respiratory society/American thoracic society technical standard: Field walking tests in chronic respiratory disease. European Respiratory Journal 44: 1428–1446.
Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, Zhou X, Liu X, Huang X, Yuan S et al. 2020 Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respiratory Research 21: 1–10.
Hu B, Guo H, Zhou P, Shi ZL 2021 Characteristics of SARS-CoV-2 and COVID-19. Nature Reviews Microbiology 19: 141–154.
Johnson JD, Theurer WM 2014 A stepwise approach to the interpretation of pulmonary function tests. American Family Physician 89: 359–366.
Kang Z, Li X, Zhou S 2020 Recommendation of low-dose CT in the detection and management of COVID-2019. European Radiology 30: 4356–4357.
Katayama K, Amann M, Pegelow DF, Jacques AJ, Dempsey JA 2007 Effect of arterial oxygenation on quadriceps fatigability during isolated muscle exercise. American Journal of Physiology Regulatory Integrative Comperative Physiology 292: 1279–1286.
Klok FA, Boon G, BarcoS E, M GJ, Knauss S, Rezek SA, Spurit MA, Vehreschild J, Siegerink B 2020 The Post-COVID-19 functional status scale: A tool to measure functional status over time after COVID-19. European Respiratory Journal 56: 2001494.
Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH 1999 Impaired chronotropic response to exercise stress testing as a predictor of mortality. Journal of American Medical Association 281:524–529.
Laughlin MH, Davis MJ, Secher NH, van Lieshout JJ, Arce-Esquivel AA, Simmons GH, Duncker DJ 2012 Peripheral circulation. Comprehensive Physiology 2: 321–447.

Lizzi F, Agosti A, Brero F, Cabini RF, Fantacci ME, Figini S, Lascialfari A, Laruina F, Oliva P, Piffer S et al. 2022 Quantification of pulmonary involvement in COVID-19 pneumonia by means of a cascade of two U-nets: Training and assessment on multiple datasets using different annotation criteria. International Journal of Computer Assisted Radiology and Surgery 17: 229–237.

Longobardi I, DMLD P, Goessler KF, Meletti MM, de Oliveira Júnior GN, de Andrade DCO, Gualano B, Roschel H 2022 Oxygen uptake kinetics and chronotropic responses to exercise are impaired in survivors of severe COVID-19. American Journal of Physiology Heart Circulation Physiology 323: 569–576.

Louvaris Z, Chynkiamis N, Spetsioti S, Asimakos A, Zakynthinos S, Wagner PD, Vogiatzis I 2020 Greater exercise tolerance in COPD during acute interval, compared to equivalent constant-load, cycle exercise: Physiological mechanisms. Journal of Physiology, Paris 598: 3613–3629.

Louvaris Z, Kortianou EA, Spetsioti S, Vasilopoulou M, Nasis I, Asimakos A, Vogiatzis I 2013 Intensity of daily physical activity is associated with central hemodynamic and leg muscle oxygen availability in COPD. Journal of Applied Physiology 115: 794–802.

Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, Dekhuijzen PN, Franssen F, Gayan-Ramirez G, Gea J, et al. 2014 An official American thoracic society/European respiratory society statement: Update on limb muscle dysfunction in chronic obstructive pulmonary disease. American Journal of Respiratory Critical Care Medicine 189: 15–62.

Mapelli M, Salvioni E, Mattavelli I, Gugliandolo P, Bonomi A, Palermo P, Rossi M, Stolfo D, Gustafsson F, Piepoli M, et al. 2023 Activities of daily living in heart failure patients and healthy subjects: When the cardiopulmonary assessment goes beyond traditional exercise test protocols. European Journal of Preventive Cardiology 30: 47–53.

Milani M, JGPO M, Cipriano GFB, Cahalin LP, Stein R, Cipriano G 2023 Cardiopulmonary exercise testing in post-COVID-19 patients: Where does exercise intolerance come from? Arquivos Brasileiros de Cardiologia 120: e20220150.

Mittal J, Ghosh A, Bhatt SP, Anoop S, Ansari IA Misra A 2021 High prevalence of post COVID-19 fatigue in patients with type 2 diabetes: A case-control study. Diabetes & Metabolic Syndrome 15: 102302.

Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, Lei C, Chen R, Zhong N, Li S 2020 Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. European Respiratory Journal 55: 2001217.

Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS et al. 2021 Post-acute COVID-19 syndrome. Nature Medicine 27: 601–615.

Omar A, Ferreira AS, Hegazy FA, Alaparthi GK 2023 Cardiorespiratory response to six-minute step test in post COVID-19 patients-a cross sectional study. Healthcare 11: 1386.

Østergaard L 2021 SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia, and inflammation. Physiological Reports 9: e14726.

Paneroni M, Simonelli C, Saleri M, Bertacchini L, Venturelli M, Troosters T, Ambrosino N, Vitacca M 2021 Muscle strength and physical performance in patients without previous disabilities recovering from COVID-19 pneumonia. American Journal of Physical Medicine Rehabilitation 100: 105–109.

Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, et al. 2020 Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology 295: 715–721.

Poole DC, Wilkerson DP, Jones AM 2008 Validity of criteria for establishing maximal O_2 uptake during ramp exercise tests. European Journal of Applied Physiology 102: 403–410.

Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, Okell T, Sheerin F, Xie C, Mahmod M, et al. 2021 Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine 31: 100683.

Romer LM, Haverkamp HC, Amann M, Lovering AT, Pegelow DF, Dempsey JA 2007 Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. American Journal of Physiology Regulatory Integrative Comparative Physiology 292: 598–606.

Sacristán-Galisteo C, Ríos-León M, Martín-Casas P, Plaza-Manzano G, López-de-Uralde-Villanueva I 2022 Construct validity of the Spanish version of the Post-COVID-19 functional status scale and validation of the web-based form in COVID-19 survivors. Public Library of Science ONE 17:e0269274.

Saleh J, Peyssonnaux C, Singh KK, Edeas M 2020 Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. Mitochondrion 54: 1–7.

Seifi S, Khatony A, Moradi G, Abdi A, Najafi F 2018 Accuracy of pulse oximetry in detection of oxygen saturation in patients admitted to the intensive care unit of heart surgery: Comparison of finger, toe, forehead and earlobe probes. BMC Nursing 17:15.

Shang C, Liu Z, Zhu Y, Lu J, Ge C, Zhang C, Li N, Jin N, Li Y, Tian M et al. 2022 SARS-CoV-2 causes mitochondrial dysfunction and mitophagy impairment. Frontiers in Microbiology 12: 780768.

Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB 2022 Persistent exertional intolerance after COVID-19: Insights from invasive cardiopulmonary exercise testing. Chest 161: 54–63.

Soares MN, Eggelbusch M, Naddaf E, Gerrits KHL, van der Schaaf M, van den Borst B, Joost Wiersinga W, van Vugt M, Weijs PJM, Murray AJ 2022 Skeletal muscle alterations in patients with acute covid-19 and post-acute sequelae of covid-19. Journal of Cachexia, Sarcopenia and Muscle 13: 11–22.

Thompson WR Gordon NF, Pescatello LS 2010 ACSM's guidelines for exercise testing and prescription (8th ed), p. 53–54. Philadelphia: Lippincott Williams & Wilkins.

Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, Solis-Navarro L, Burgos F, Puppo H, Vilaró J 2021 Respiratory function in patients post-infection by COVID-19: A systematic review and meta-analysis. Pulmonology 27: 328–337.

Toussie D, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, Jacobi A, Chung M, Bernheim A, Eber C, et al. 2020 Clinical and chest radiography features determine patient outcomes in young and middle-aged adults with COVID-19. Radiology 297: 197–206.

Tudor-Locke C, Bassett DR 2004 How many steps/day are enough? Sports Medicine 34: 1–8.

Watz H, Waschki B, Meyer T, Magnussen H 2008 Physical activity in patients with COPD. European Respiratory Journal 332: 262–272.

Yılmaz Demirci N, Uğraş Dikmen A, Taşçı C, Doğan D, Arslan Y, Öcal N, Taşar M, Bozlar U, Artuk C, Yılmaz G, et al. 2021 Relationship between chest computed tomography findings and clinical conditions of coronavirus disease (COVID-19): A multicentre experience. International Journal of Clinical Practice 75: e14459.

Zaim S, Chong JH, Sankaranarayanan V, Harky A 2020 COVID-19 and multiorgan response. Current Problems in Cardiology 45: 100618.