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Cardiopulmonary Exercise Testing in Critically Ill Coronavirus Disease 2019 Survivors: Evidence of a Sustained Exercise Intolerance and Hypermetabolism

Maurice Joris, MD[1]
Pauline Minguet, RN[2]
Camille Colson, RN[2]
Jean Joris, MD, PhD[3,4]
Marjorie Fadeur, RD[4]
Gregory Minguet, MD, PhD[3]
Julien Guiot, MD, PhD[5]
Benoit Misset, MD[2]
Anne-Françoise Rousseau, MD PhD[2,4]

OBJECTIVES: To investigate exercise capacity at 3 and 6 months after a prolonged ICU stay.

DESIGN: Observational monocentric study.

SETTING: A post-ICU follow-up clinic in a tertiary university hospital in Liège, Belgium.

PATIENTS: Patients surviving an ICU stay greater than or equal to 7 days for a severe coronavirus disease 2019 pneumonia and attending our post-ICU follow-up clinic.

MEASUREMENTS AND MAIN RESULTS: Cardiopulmonary and metabolic variables provided by a cardiopulmonary exercise testing on a cycle ergometer were collected at rest, at peak exercise, and during recovery. Fourteen patients (10 males, 59 yr [52–62 yr], all obese with body mass index $> 27\,kg/m^2$) were included after a hospital stay of 40 days (35–53 d). At rest, respiratory quotient was abnormally high at both 3 and 6 months (0.9 [0.83–0.96] and 0.94 [0.86–0.97], respectively). Oxygen uptake was also abnormally increased at 3 months (8.24 mL/min/kg [5.38–10.54 mL/min/kg]) but significantly decreased at 6 months ($p = 0.013$). At 3 months, at the maximum workload (67% [55–89%] of predicted workload), oxygen uptake peaked at 81% (64–104%) of predicted maximum oxygen uptake, with oxygen pulse and heart rate reaching respectively 110% (76–140%) and 71% (64–81%) of predicted maximum values. Ventilatory equivalent for carbon dioxide remains within normal ranges. The 50% decrease in oxygen uptake after maximum effort was delayed, at 130 seconds (115–142 s). Recovery was incomplete with a persistent anaerobic metabolism. At 6 months, no significant improvement was observed, excepting an increase in heart rate reaching 79% (72–95%) ($p = 0.008$).

CONCLUSIONS: Prolonged reduced exercise capacity was observed up to 6 months in critically ill coronavirus disease 2019 survivors. This disability did not result from residual pulmonary or cardiac dysfunction but rather from a metabolic disorder characterized by a sustained hypermetabolism and an impaired oxygen utilization.

KEY WORDS: cardiopulmonary exercise testing; coronavirus disease 2019; critical illness; hypermetabolism; survivors

Due to continuous improvements in critical care, an increasing number of patients survive acute severe diseases, organ failures, and ICU stay. ICU survivors may experience several new or worsening disorders that negatively affect their daily functioning and quality of life, classically named the postintensive care syndrome (1). Functional impairments may persist up to 5 years following ICU discharge (2). Acute respiratory distress

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syndrome (ARDS) survivors recover more slowly than non-ARDS survivors (3).

Loss of physical function is the most frequently reported disabling complaint among ICU survivors (4, 5). Exercise capacity depends on muscle mass and function, on oxygen transport from air to mitochondria, and on its use during muscle work. Muscle abnormalities after critical illness are called ICU-acquired weakness. This is a complex association of muscle wasting, impaired homeostasis of muscle proteins, changes in muscle composition, impaired regeneration, derangement in excitation-contraction coupling, and acquired mitochondrial dysfunction (6, 7).

Cardiopulmonary exercise testing (CPET) is the most objective technique to assess exercise capacity (8). It provides an integrative assessment of the responses to exercise of the pulmonary, cardiovascular, metabolic, and skeletal muscle systems. This noninvasive, dynamic physiologic evaluation involves measurements of respiratory oxygen uptake (Vo_2), carbon dioxide output (Vco_2), ventilation, and metabolism as well as routine physiologic and performance variables during a symptom-limited incremental exercise test. Although this methodology provides a markedly increased amount of information compared with more conventional functional tests, there are still very few studies reporting CPET after critical illness (9–11).

About 5% of patients affected by the severe acute respiratory syndrome coronavirus-2 require critical care for ARDS (12). It has been demonstrated that coronavirus disease 2019 (COVID-19) ARDS reproduces the pathophysiology of ARDS from other etiologies after initiation of invasive ventilation (12). According to the few published data, the short- and mid-term physical consequences of a severe COVID-19 pneumonia seems to be considerable (13, 14) (data of our center are under revision).

The primary aim of this observational monocentric study was to assess exercise capacity using CPET in COVID-19 ARDS survivors, 3 months (M3) after ICU discharge. We coupled CPET to a measure of the body composition, in order to get a complete picture of the patients status. The second aim was to describe the natural course of the physical performances 3 months later, at 6 months (M6) after ICU discharge.

METHODS

Patients and Data sources

In our university hospital, patients surviving an ICU stay greater than or equal to 7 days are routinely invited to our postintensive care follow-up clinic, 1, M3, M6, and 12 months after ICU discharge. Each visit is performed by a multidisciplinary team, including a critical care physician, a critical care nurse, a physiotherapist, and a dietician. The content examination is standardized, addressing physical status and functional performances, mental health disorders, cognitive impairment, sleep disorders, and health-related quality of life. During the COVID-19 pandemic, an assessment of exercise capacity, performed at the Sports Medicine Unit of the Province of Liège at M3 and M6 after ICU discharge, was added to the standardized follow-up. The two appointments (follow-up clinic and exercise capacity assessment) were scheduled on different days.

In accordance with Belgian law, informed consent was not required because the study did not modify patients' management and the data were anonymously collected. This was confirmed by the Ethics Committee of the University Hospital of Liege, Belgium (chair: Professor V. Seutin, local reference 2020/424).

Measurements

Physical performances were prospectively recorded during the assessment of exercise capacity at the Sports Medicine Unit using CPET at M3 and M6. Body composition using bioelectrical impedance was also determined at both time points.

Patients' characteristics and clinical data related to their ICU stay were collected retrospectively and extracted from the medical charts.

Bioelectrical Impedance

Total body fat, fat-free mass, and water composition were measured using bioelectrical impedance with a Tanita MC-780 multifrequency segmental body composition analyzer (Tanita Europe, Amsterdam, the Netherlands), a stand-alone unit. The quality control and calibrations were realized as described by the manufacturer before each examination.

CPET

Patients underwent a symptom-limited, incremental CPET on a cycle ergometer (Corival CPET 960900; Lode BV, Groningen, the Netherlands) under the supervision of a trained sports physician. All the tests and calculations were realized by the same investigator (M.J.) to reduce interindividual variability. Patients were asked to continue their usual medications before the test. The protocol consisted of a 3-minute warm-up with a fixed workload (30% of the predicted maximum workload). A personalized ramp increment in workload of 15–25 Watts every 2 minutes was then started and continued until exhaustion, defined as shortness of breath and/or leg fatigue. This was followed by 3 minutes of recovery. Ventilation and gas exchange variables were measured using a metabolic cart (Schiller Cardiovit CS-200 Excellence; Schiller AG, Baar, Switzerland). Calibrations were realized two times a day, according to manufacturer's instructions.

Pulmonary flow volumes, including measurement of forced expiratory volume in 1 second (FEV1), were determined before CPET by spirometry in a sitting position, as recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (15). CPET was performed and interpreted based on ATS/American College of Chest Physicians guidelines (16). Vo_2, Vco_2, and minute ventilation (VE) were measured breath-by-breath during CPET. One metabolic equivalent (MET) is the resting Vo_2 in a sitting position and equals 3.5 mL/kg/min. Patients around 60 years old typically reach seven or eight MET at effort. Ventilatory equivalent for Co_2 (Veq Co_2) assessed the ventilatory efficiency (= VE/Vco_2). At rest, Veq Co_2 is typically between 25 and 30. The anaerobic threshold (AT) is defined as the highest Vo_2 attained without a sustained increase in blood lactate concentration and lactate-pyruvate ratio. It is detected metabolically as the point of inflection at which Vco_2 and VE increase relative to Vo_2. AT occurs typically between 47% and 64% of the peak Vo_2 in healthy untrained individuals. The respiratory exchange ratio (RER) is defined as follows: RER = Vco_2/Vo_2. An RER of 1 indicates a metabolism using primarily of carbohydrates, whereas an RER less than 1 results from a metabolism using a mixture of carbohydrates with fat (RER ~ 0.7) or protein (RER ~ 0.8). Heart rate (HR), 12-lead electrocardiogram (ECG), noninvasive blood pressure, and pulse oximetry were monitored throughout. Oxygen pulse (πo_2), a surrogate of stroke volume, was calculated by dividing Vo_2 by HR, as is typically around 5 mL/beat in healthy nonathletes.

Maximum predicted Vo_2 (a measurement of the maximal aerobic capacity) was calculated using Wasserman equation. Maximum predicted HR was calculated using the Astrand formula: HR maximum predicted = 220–age (yr). The breathing reserve (BR) at maximum exercise was calculated as maximum voluntary ventilation (MVV) minus ventilation at maximum of exercise (peak VE), and the result was divided by MVV ([MVV–peak VE]/MVV). In this protocol, MVV was calculated by multiplication of FEV1 value × 30. BR refers to how closely VE approaches MVV during exercise and is typically greater than or equal to 20% (between 30% and 50%) in healthy nonathletes. The chronotropic response (CR) to exercise was evaluated by the percentage of chronotropic reserve (% chronotropic reserve = [peak HR–resting HR/220–age–resting HR] × 100). It is typically greater than 85% in healthy nonathletes. Metabolic efficiency was calculated as workload (converted in ml oxygen/min) divided by peak Vo_2 and is typically between 15% and 35% in healthy nonathletes.

Baseline data were recorded during the resting period. Peak data were recorded during the last 20 seconds of the test. The normal value for peak Vo_2 is greater than 84% of the maximum predicted Vo_2. The peak πo_2 is typically greater than 80% of the maximum predicted πo_2. T1/2, that is, the time required for a 50% decrease in Vo_2 from its peak value, was also recorded: it typically occurs 80 seconds after the end of effort in healthy nonathletes.

Clinical Status at M3

Clinical data about respiratory status, as well as biological variables related to inflammation and endocrine status, were prospectively collected following attendance at M3 consultation at our follow-up clinic.

Dyspnea was evaluated using the Modified Medical Research Council Dyspnea Scale. Lung function tests were performed in the respiratory laboratory of our hospital. The spirometric tests were performed using the pneumotachograph Jaeger Master labsystem (Erich Jaeger GmbH, Wuzburg, Germany). The FEV1 and forced vital capacity were measured in accordance with

the recommendations of the ERS (17). The results were expressed in percent predicted. The diffusion capacity of carbon oxide (DLCO) was measured by the single-breath carbon monoxide gas transfer method and expressed as percent predicted (SensorMedics2400He/CO Analyzer System; Sensor Medics, Bilthoven, the Netherlands).

The biological data were generated from one single laboratory (Unilab, CHU de Liège) accredited for ISO 15189 Guideline. The following biomarkers were recorded: serum C-reactive protein (CRP), serum thyroid-stimulating hormone (TSH) and thyroxine (T4), and serum cortisol (immunoassays, Abbott Alinity instrument). These analyses are part of our routine follow-up. Blood samples were collected in the early afternoon. The normal ranges are 0–5 mg/L for CRP, 0.35–4.94 mUI/L for TSH, 8.7–16.8 pmol/L for T4, and 80–477.3 nmol/L for cortisol.

The functional status prior to ICU admission was retrospectively assessed at the M3 consultation. Physical activity status was characterized according to the patient's self-report: patients who reported recreational physical activity or sports activity for 4 or more hours per week were considered physically active, whereas patients who did not achieve this were considered physically inactive. Pre-ICU independence for daily living activities was evaluated using the Barthel Index (18).

Statistical Analyses

Statistical analysis was performed using Graphpad Prism (Version 9.0 for Mac OSX; Graphpad, San Diego, CA). Normality was assessed using the Shapiro-Wilk test. Characteristics of patients were described as median (interquartile range) or count (percent) for quantitative and qualitative variables, respectively. Comparisons between time points were made using Wilcoxon test. Comparisons of bioelectrical impedance and CPET variables between patients who did or did not completed inpatient rehabilitation after hospital discharge were made using Mann-Whitney *U* test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

From March 1, 2020, to July 17, 2020, 42 patients with COVID-19 ARDS survived an ICU stay greater than or equal to 7 days. Eighteen of these patients attended the sports medicine consultation at M3 and were able to performed the CPET. Four patients were then lost to follow-up. Finally, 14 patients performed the CPET and were analyzed (**Fig. 1**). Descriptive characteristics of the included subjects are detailed in **Table 1**. Most patients (11/14; 78.6%) were treated by selective beta-blockers at testing time. At M3, half of them had no residual dyspnea, lung volumes were not limited, and DLCO was slightly reduced. No fever or endocrine abnormalities were observed at M3 (**Table 2**).

Body Composition

Patient's body composition at M3 and M6 is detailed in **Table 3**. Patients were all considered obese at M3, and their body mass index even increased at M6, with a significant increase in fat mass and a significant decrease in muscle mass (Table 3). Body water was low at M3 and decreased further at M6 (Table 3).

CPET: Resting State

At rest at M3, Vo_2 and RER were increased compared with normal ranges in healthy people (**Fig. 2**). Similarly, MET was abnormally high. At M6 at rest, RER remained high, whereas Vo_2 significantly decreased compared with M3 (Fig. 2). MET also significantly decreased at M6 (**Supplementary Table 1**, http://links.lww.com/CCX/A723). Veq Co_2 was into normal ranges and did not change between M3 and M6 (Fig. 2). HR, pulse oxygen saturation (Spo_2), and πo_2 at baseline at both time points are described in Supplementary Table 1 (http://links.lww.com/CCX/A723).

CPET: Adaptations to Effort

Physiologic adaptations to effort started early, after 2.7 minutes (1.8–4.1 min) at M3 and after 2.7 minutes (1.9–5.2 min) at M6 (p = 0.856). At M3 as at M6, it occurred for a workload of 40% (30–55%) of the maximal predicted workload (161 Watts [137–178 Watts] at M3 and 172 Watts [139–195 Watts] at M6).

All patients reported to have performed a maximal volitional effort up to their limits, but effort was stopped before reaching maximal predicted workload and maximal predicted Vo_2 (27.1 mL/min/kg [18.6–29.7 mL/min/kg] at M3 and 26.4 mL/min/kg [18.3–28.1 mL/min/kg] at M6).

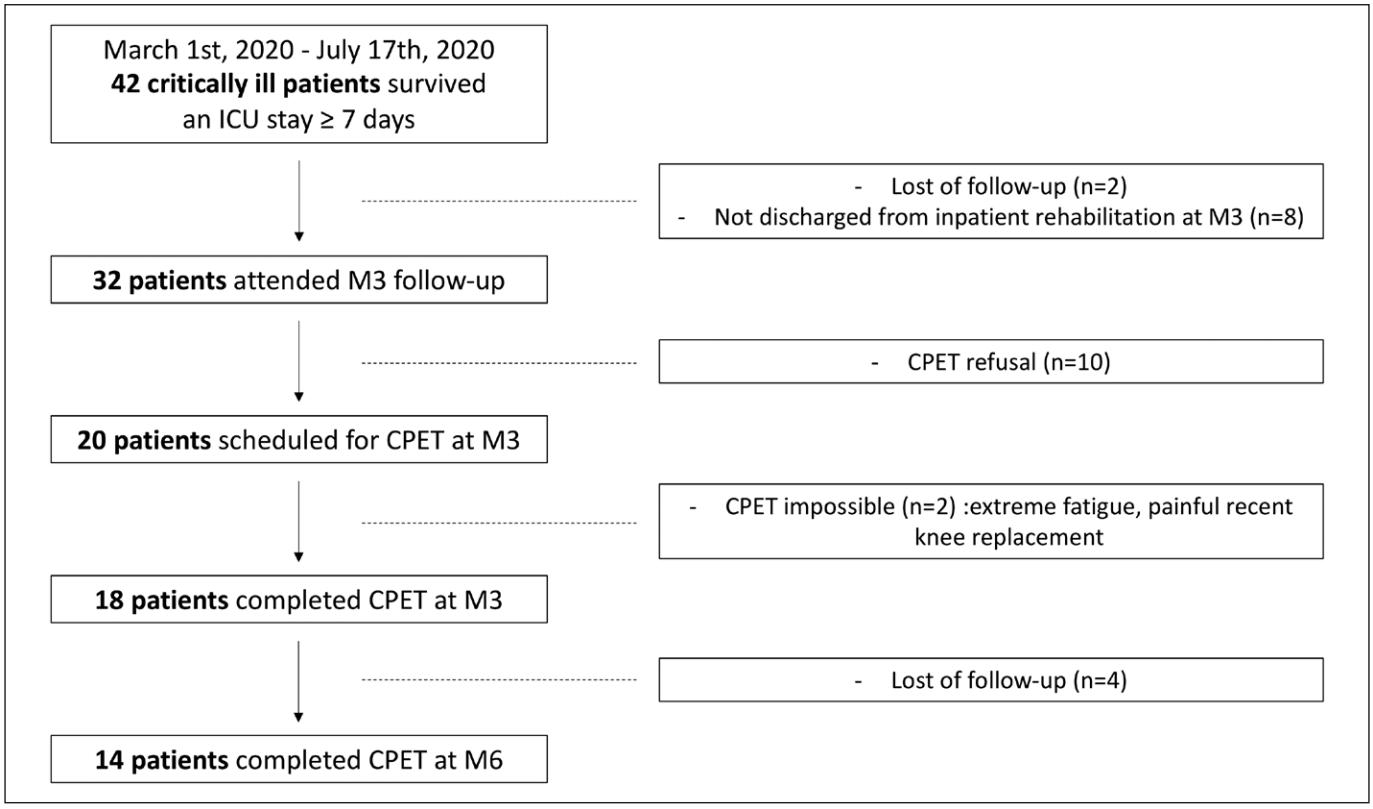

Figure 1. Flow chart. CPET = cardiopulmonary exercise testing, M3 = 3 mo, M6 = 6 mo.

The AT was observed at 77.5% (70.2–82%) of the peak Vo_2 at M3 and at 71.5 (66.6–79.4) % of the peak Vo_2 at M6 ($p = 0.086$).

At maximum effort, the workload reached was higher at M6 compared with M3 ($p = 0.006$): 135 Watts (85–170 Watts) and 115 Watts (57.5–146.3 Watts), respectively, corresponding to 67% (55–89%) and 63% (39–93%) of maximum predicted workload, respectively. At M3 and M6, peak Vo_2 reached 81% (64–104%) and 80% (64–102%) of the maximal predicted Vo_2, respectively ($p = 0.903$) (Fig. 2). Peak RER was above 1.0, which means anaerobic metabolism activation and hyperventilation were involved (Fig. 2). Peak Veq Co_2 did not significantly increase during exercise compared with resting state ($p = 0.761$ and $p = 0.296$ at M3 and M6, respectively) (Fig. 2). πo_2 significantly increased at effort compared with resting state ($p < 0.001$ at both M3 and M6) (Supplementary Table 1, http://links.lww.com/CCX/A723). At M3 and M6, peak πo_2 reached 110% (76–140%) and 101% (82–133%) of the maximum predicted πo_2, respectively ($p = 0.079$). Spo_2 significantly decreased at the end of the effort, compared with values at rest ($p = 0.004$ and $p = 0.003$ at M3 and M6, respectively) (Supplementary Table 1, http://links.lww.com/CCX/A723). Peak HR reached 71% (64–81%) and 79% (72–95%) of the maximal predicted HR at M3 and M6, respectively ($p = 0.008$). Their maximal predicted HR was 160 beats/min (158–168 beats/min). Absolute HR values are described in Supplementary Table 1 (http://links.lww.com/CCX/A723). CR was under normal values at both M3 and M6 (Supplementary Table 1, http://links.lww.com/CCX/A723). On the contrary, BR was considered normal at both the two time points (Supplementary Table 1, http://links.lww.com/CCX/A723).

Metabolic efficiency was quite low at M3: 15% (13–18%). Although a small significant increase was observed at M6, reaching 18% (16–20%) ($p = 0.017$), it remained below normal ranges.

Despite the severe deconditioning diagnosed in these patients, no adverse events were noticed during CPET examination.

CPET: Recovery After Effort

During recovery, T1/2 was reached later than its predictable timing: 130 seconds (115–142 s) after the end of the effort at M3. No significant improvement

TABLE 1.
Characteristics of the Included Patients

Data		*N* = 14
Age, yr, median (interquartile range)		59 (52–62)
Male, *n* (%)		10 (71)
Physical inactivity prior to ICU admission, *n* (%)		10 (71)
Barthel index prior to ICU admission, median (interquartile range)		100 (100–100)
Comorbidity, *n* (%)	Hypertension	7 (50)
	Diabetes	5 (37.7)
	Cardiac	4 (28.6)
	Respiratory	4 (28.6)
	Active smoker	1 (7.1)
	Chronic kidney disease	1 (7.1)
Sequential Organ Failure Assessment at admission, median (interquartile range)		7 (3.7–8.7)
Mechanical ventilation, *n* (%)		14 (100)
Tracheostomy, *n* (%)		3 (21.4)
Duration of mechanical ventilation, d, median (interquartile range)		19 (12–30)
Steroids during ICU stay, *n* (%)		10 (71)
Renal replacement therapy, *n* (%)		3 (21.4)
ICU LOS, d, median (interquartile range)		24 (15–41)
Hospital LOS, d, median (interquartile range)		40 (35–53)
Discharge destination, *n* (%)	Home	7 (50)
	Rehabilitation inpatient facility	7 (50)
Rehabilitation LOS, d, median (interquartile range)		25 (20–34)

LOS = length of stay.

TABLE 2.
Clinical Status at 3 Months

Data		*N* = 14
Modified Medical Research Council Dyspnea Scale score, *n* (%)	0	7 (50)
	1	6 (43)
	2	1 (7)
Fever, *n* (%)		0
Forced vital capacity, % predicted, median (interquartile range)		84 (78–110)
Forced expiratory volume in 1 s, % predicted, median (interquartile range)		89 (82.5–106.5)
Diffusion capacity of carbon monoxide, % predicted, median (interquartile range)		71 (52.7–82.5)
C-reactive protein, mg/L, median (interquartile range)		1.95 (0.95–2.69)
Thyroid-stimulating hormone, mUI/L, median (interquartile range)		1.05 (0.49–1.75)
Thyroxine (T4), pmol/L, median (interquartile range)		10.95 (9.82–13.23)
Cortisol, nmol/L, median (interquartile range)		210.9 (152.4–267.8)

TABLE 3.
Body Composition, at 3 and 6 Months

Data, Median (IQR)	3 mo	6 mo	*p*
Body mass index (kg/m²)	32.3 (30.2–35.2)	33.8 (31.8–36.2)	0.001
Fat mass (% body mass)	27.5 (25.1–35.9)	31.2 (27.7–37.3)	< 0.001
Muscle mass (% body mass)	68.9 (60.8–71.2)	65.3 (59.4–68.8)	< 0.001
TBW (% body weight)	51.3 (44.8–54.4)	49.2 (43.4–51.3)	< 0.001
Extracellular water (% TBW)	42.25 (41.1–45.2)	42.9 (41.7–45.4)	0.008
Intracellular water (% TBW)	57.75 (54.8–58.9)	57 (54.6–58.2)	0.008

IQR = interquartile range, TBW = total body water.

was observed at M6 (p = 0.951): 120 minutes (100–167 min). As described in Figure 2, RER still increased at T1/2, as well as Veq Co_2. HR, Spo_2, and πo_2 evolution at T1/2 at both time points are described in Supplementary Table 1 (http://links.lww.com/CCX/A723). At M3 and M6, 4 minutes after the end of the effort, on ECG, QTc interval was 421 ms (397–442 ms) and 359 ms (321–421 ms), respectively (p = 0.064).

Comparisons Between Patients Who Did or Did Not Completed Inpatients Rehabilitation After Hospital Discharge

At M3, muscle mass, resting RER, peak Vo_2 and Veq Co_2, percentage of maximal predicted workload, and timing for T1/2 were not statistically different between the two groups of patients.

DISCUSSION

Using CPET, we investigated the recovery course of exercise capacity after ICU discharge in a homogeneous

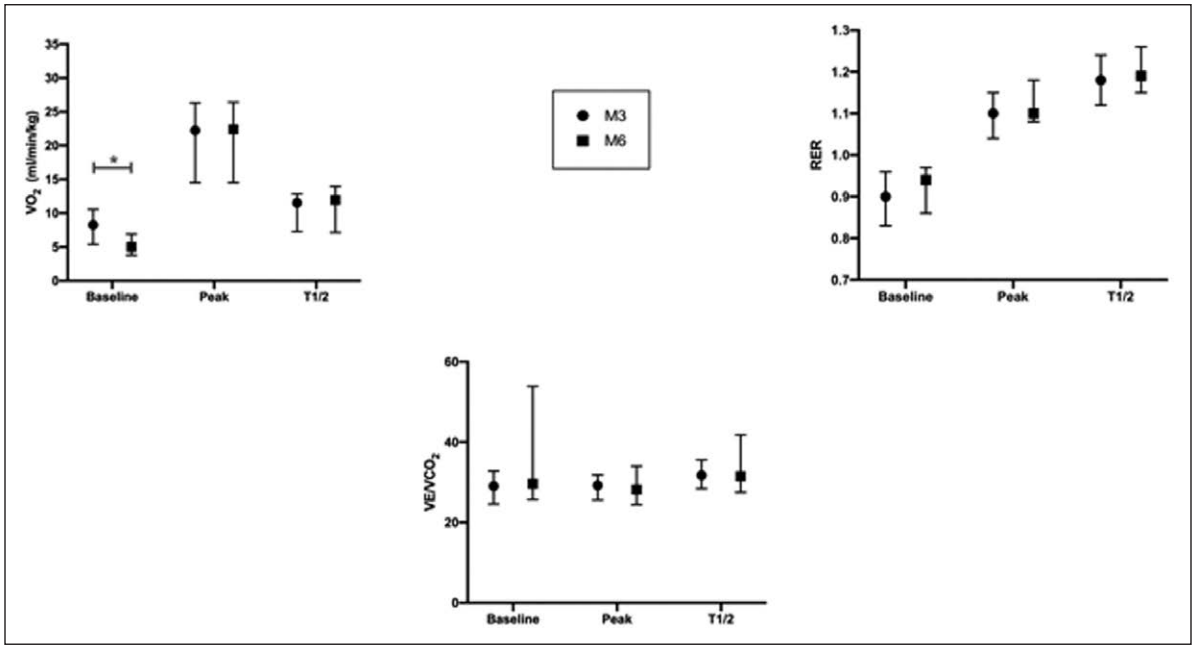

Figure 2. Oxygen uptake (Vo_2), ventilatory equivalent for carbon dioxide (minute ventilation [VE]/carbon dioxide output [Vco_2]), and respiratory exchange ratio changes during exercise testing, at the two time points (3 mo [M3], *black circle* and 6 mo [M6], *black square*). Data are expressed as median and interquartile ranges (*$p < 0.05$) RER = respiratory exchange ratio.

cohort of COVID-19 ARDS survivors. Our study demonstrates a prolonged reduced exercise capacity associated with metabolic troubles, lasting at least M6 after ICU discharge.

Patients were all obese, and their fat mass increased over time, at the expenses of muscle mass. At rest, a hypermetabolic status was observed (i.e., high baseline Vo_2 and MET) that slightly diminished at M6. We did not observe any acute infection or endocrine abnormalities as other cause of elevated basal metabolism. Patients used proteins as metabolic fuel, rather than lipids, as suggested by baseline elevated RER, both at M3 and M6. Their exercise capacity was reduced, as the maximum workload reached approximately two third of the maximum predicted workload, with a disproportionate oxygen consumption corresponding to three quarters of the maximum predicted Vo_2. Despite the risk of subclinical myocardial inflammation described after COVID-19 (19), cardiac response seemed appropriate with a normal πo_2 profile and an appropriate chronotropic adaptation, despite the treatment with selective beta-blockers administered to most patients. Furthermore, the profile of Veq Co_2 was normal, which ruled out any right ventricular dysfunction that could have persisted after ARDS. Metabolic efficiency was dramatically low at 3 months and only slightly increased at M6. Recovery after effort was quite slow and incomplete, with a persistent anaerobic metabolism. This probably contributed to lower the metabolic reserves, explaining why physiologic adaptations to effort occurred early. A hyperventilation was observed that can be explained by the low metabolic efficiency. This is probably associated with an increased thermogenesis and a subsequent loss of water, justifying the observed low total body water. No significant improvement in recovery was observed 3 months later. Especially at M6, QTc were still short 4 minutes after the end of the effort, suggesting a high sympathetic tone. Altogether, results of CPET suggest that this exercise disability cannot be explained by insufficient oxygen delivery secondary to persistent impairment of pulmonary or cardiac function, but rather by a metabolic disorder. Indeed, these patients presented signs of sustained hypermetabolism and impaired oxygen utilization.

A reduced exercise capacity without pulmonary impairment has been observed in a small number of COVID survivors including five patients who benefited from mechanical ventilation (20) and in non-COVID ARDS survivors (10). Although poorly investigated in general ICU survivors, abnormal metabolic patterns have been well described after severe burn injuries and may persist at least 2 years after a severe burn (21). Recently in one burn survivor who performed a CPET, some authors reported similar metabolic abnormalities than those observed in the present study (22): 6 months after injury, the patient was still unable to use fat for energy in his muscle.

In the present study, we observed a sustained hypermetabolism status at rest with RER indicating metabolism primarily of protein. Hypermetabolism after a critical illness or injury is driven by inflammation and neuroendocrine stress response and results in numerous pathophysiologic alterations: supraphysiologic metabolic rates, proteolysis, lipolysis, insulin resistance, gluconeogenesis, and futile substrate cycling (23, 24). Furthermore, the body fails to recognize fat as source of energy and rather uses proteins as major fuel, leading to muscle protein breakdown and loss of muscle mass, due to the use of proteins as the primary fuel (25). We also observed a failure in oxygen utilization, potentially originating in the presence of a microangiopathy with disturbed oxygen extraction, or an alteration of mitochondrial function. Indeed, mitochondrial dysfunction is observed as early as acute phase of a critical illness, at least in the muscles (26). A dysregulated lipid oxidation seems to contribute to compromised skeletal muscle bioenergetic status in early critical illness (27). This mitochondrial dysfunction has been linked to the severity of illness and related mortality (28, 29). Recent data in an animal model of sepsis suggested that mitochondrial dysfunction was sustained in survivors, explaining why mice experienced profound muscle weakness despite the recovery of their muscle mass (30). This is the basis of the theory of adaptive mitochondrial metabolic-bioenergetic down-regulation (31). Our findings are in agreement on this theory. Mitochondria is considered as a final common point of stress response pathways (32). Mitochondrial dysfunction has been linked to inflammation and oxidative stress, two common features in ICU patients (33) and in critically ill COVID-19 patients (34). Inflammation persists in ICU survivors (35, 36). In this study, only CRP was used to measure inflammation, and values were into normal ranges. However, other data suggest CRP might decrease

more rapidly than other biomarkers of inflammation such as interleukins (37), emphasizing the interest of a multimodal assessment. In critically ill COVID-19 survivors, we recently measured biomarkers of the systemic oxidative stress status including enzymatic and nonenzymatic antioxidants, total antioxidant capacity of plasma (PAOT technology; European Institute of Antioxidants), trace elements, oxidative damage to lipids, and inflammation markers. Within the 2 months following ICU discharge, we observed a heightened blood oxidative stress with a severe depletion in main antioxidants and an increased level in myeloperoxidase (submitted data).

Persistent use of proteins as energy source instead of lipids at rest, hypermetabolism, crashed metabolic efficiency, and altered metabolic recovery after effort can lead to exhaustion of the metabolic reserves and muscle mass. In other words, it seems illusory to regain muscle strength and exercise capacity until deficiencies in muscle quality and hypermetabolism are addressed. Multimodal approach could be considered, including nonselective beta-adrenergic receptor antagonist (propranolol) to fight the catecholamine surge and the subsequent hypermetabolism, anabolic agents to counteract catabolic response (e.g., oxandrolone), and adequate nutrition to provide appropriate macro- and micronutrients intakes, including antioxidant micronutrients supplementation (25). This should probably be the first step prior initiation of individualized exercise training (9). Some of these strategies are commonly and safely used after severe burn injury, a model of intense and prolonged systemic response after critical illness and injury (38–40). Modulation of hypermetabolism and oxidative stress are unfortunately rarely investigated in nonburn critically ill patients. Similarly, the potential benefits of anti-inflammatory drugs are unquantified in postintensive care syndrome (41). There is an urgent need for further investigation in these topics, in order to improve functional outcomes in ICU survivors.

This study surely extends the knowledge regarding exercise capacity and metabolic dysfunction throughout a comprehensive, objective, and integrative method of physical performances assessment. However, some limitations need to be acknowledged. First, the cohort was limited. This could explain the absence of pulmonary or cardiac limitations in the studied cohort, unlike other contradictory observations in other studies (42). Furthermore, it is possible that only the fittest patients accepted the CPET. This is an inherent selection bias of a follow-up studies. Second, the cohort focused only on COVID-19 ARDS survivors, without any control group. It would be interesting to compare the present results with non–COVID-19 critically ill survivors, noncritical COVID-19 patients, nonobese critically ill survivors, or healthy untrained subjects: this work is ongoing in our follow-up clinic. Third, patients were not fasting before performing CPET but were advised to prefer snack or light meal if needed. Fourth, nutrition and physical activities were not standardized before each CPET and were not quantified. Finally, this study lacks precise assessment of baseline exercise capacity. It is a common issue with many studies assessing long-term outcomes in ICU survivors in general and is related to the unpredictable characteristic of ICU admissions, particularly during this pandemic. This pitfall can lead to misinterpretation of what is considered as postintensive care sequelae.

CONCLUSIONS

Exercise capacity of critically ill COVID-19 survivors was dramatically reduced 3 months after ICU discharge, mainly related to metabolic disorders rather than cardiac or pulmonary residual impairments. No major improvement was observed 3 months later, at M6. These observations could be the basis for further studies evaluating a revised rehabilitation strategy, starting with modulation of persistent inflammation, oxidative stress, and hypermetabolism before any physical training.

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1 *Department of Sports Medicine, Malvoz Institute, Province of Liège, Liège, Belgium.*

2 *Department of Intensive Care and Burn Center, University Hospital, University of Liège, Liège, Belgium.*

3 *Department of Anesthesiology, University Hospital, University of Liège, Liège, Belgium.*

4 *Multidisciplinary Nutrition Team, University Hospital, University of Liège, Liège, Belgium.*

5 *Department of Pneumology, University Hospital, University of Liège, Liège, Belgium.*

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Dr. Rousseau designed the research. Mrs. P. Minguet and Colson *coordinated the post-ICU follow-up. Dr. M. Joris conducted research. Drs. M. Joris, J. Joris, G. Minguet, Rousseau, and Mrs. Fadeur analyzed data. Dr. Rousseau wrote the draft article. Drs. M. Joris, J. Joris, G. Minguet, Misset, and Mrs. Fadeur critically reviewed the draft article. All authors approved the final article.*

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For information regarding this article, E-mail: afrousseau@chuliege.be

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