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ORIGINAL RESEARCH

Ongoing Exercise Intolerance Following COVID-19: A Magnetic Resonance–Augmented Cardiopulmonary Exercise Test Study

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BACKGROUND: Ongoing exercise intolerance of unclear cause following COVID-19 infection is well recognized but poorly understood. We investigated exercise capacity in patients previously hospitalized with COVID-19 with and without self-reported exercise intolerance using magnetic resonance–augmented cardiopulmonary exercise testing.

METHODS AND RESULTS: Sixty subjects were enrolled in this single-center prospective observational case-control study, split into 3 equally sized groups: 2 groups of age-, sex-, and comorbidity-matched previously hospitalized patients following COVID-19 without clearly identifiable postviral complications and with either self-reported reduced ($COVID_{reduced}$) or fully recovered ($COVID_{normal}$) exercise capacity; a group of age- and sex-matched healthy controls. The $COVID_{reduced}$group had the lowest peak workload (79W [Interquartile range (IQR), 65–100] versus controls 104W [IQR, 86–148]; P=0.01) and shortest exercise duration (13.3±2.8 minutes versus controls 16.6±3.5 minutes; P=0.008), with no differences in these parameters between $COVID_{normal}$ patients and controls. The $COVID_{reduced}$ group had: (1) the lowest peak indexed oxygen uptake (14.9 mL/minper kg [IQR, 13.1–16.2]) versus controls (22.3 mL/min per kg [IQR, 16.9–27.6]; P=0.003) and $COVID_{normal}$ patients (19.1 mL/min per kg [IQR, 15.4–23.7]; P=0.04); (2) the lowest peak indexed cardiac output (4.7±1.2 L/min per m^2) versus controls (6.0±1.2 L/min per m^2; P=0.004) and $COVID_{normal}$ patients (5.7±1.5 L/min per m^2; P=0.02), associated with lower indexed stroke volume (SVi:$COVID_{reduced}$ 39±10 mL/min per m^2 versus $COVID_{normal}$ 43±7 mL/min per m^2 versus controls 48±10 mL/min per m^2; P=0.02). There were no differences in peak tissue oxygen extraction or biventricular ejection fractions between groups. There were no associations between COVID-19 illness severity and peak magnetic resonance–augmented cardiopulmonary exercise testing metrics. Peak indexed oxygen uptake, indexed cardiac output, and indexed stroke volume all correlated with duration from discharge to magnetic resonance–augmented cardiopulmonary exercise testing (P<0.05).

CONCLUSIONS: Magnetic resonance–augmented cardiopulmonary exercise testing suggests failure to augment stroke volume as a potential mechanism of exercise intolerance in previously hospitalized patients with COVID-19. This is unrelated to disease severity and, reassuringly, improves with time from acute illness.

Key Words: cardiopulmonary exercise testing ■ cardiovascular magnetic resonance imaging ■ COVID-19 ■ exercise ■ stroke volume

Ongoing exercise intolerance is recognized following COVID-19, with a significant proportion of hospitalized patients reporting reduced exercise capacity after discharge.[1] In addition, reduced peak oxygen consumption (VO_2) has been demonstrated after resolution of acute COVID-19 infection.[2] This can partly

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CLINICAL PERSPECTIVE

What Is New?

- The importance of stroke volume augmentation in the normal response to exercise is emphasized by this magnetic resonance–augmented cardiopulmonary exercise test study.
- The magnetic resonance–augmented cardiopulmonary exercise test demonstrated reduced systolic blood pressure augmentation in patients who had previously been hospitalized with COVID-19 infection and with self-reported ongoing reduced exercise capacity.
- There were no magnetic resonance–augmented cardiopulmonary exercise test findings to suggest impaired contractile reserve, exercise diastolic dysfunction, or abnormalities of peak afterload in these patients, suggesting that inadequate preload could be a possible mechanism underlying reduced systolic blood pressure augmentation and, consequently, exercise intolerance.

What Are the Clinical Implications?

- The comprehensive evaluation of unexplained dyspnea and exercise intolerance is pivotal to help correctly identify potential therapeutic targets in these patients.
- Although the causes of failure to augment systolic blood pressure on exercise require further investigation in these patients, the findings do raise the possibility of interventions tailored to volume expansion being explored in future studies.
- Reassuringly, abnormalities in peak magnetic resonance–augmented cardiopulmonary exercise test metrics may improve with time from the acute illness and are unrelated to markers of disease severity.

Nonstandard Abbreviations and Acronyms

ΔavO_2	arteriovenous oxygen content gradient
CO	cardiac output
COi	indexed cardiac output
$COVID_{normal}$	normal exercise capacity following COVID-19
$COVID_{reduced}$	reduced exercise capacity following COVID-19
CPET	cardiopulmonary exercise testing
iVO_2	indexed oxygen uptake
MR	magnetic resonance
MR-CPET	magnetic resonance-cardiopulmonary exercise testing
SV	stroke volume
VO_2	oxygen consumption

be explained by residual lung parenchymal damage, myocardial injury, or sequelae from pulmonary thromboembolic disease.[3–6] However, exercise intolerance is also described in patients without clearly identifiable postviral complications.[7] In this group, possible causes include: (1) failure to augment cardiac output (CO) attributable to reduced contractile or preload reserve and; (2) impaired skeletal muscle oxygen extraction caused by skeletal muscle dysfunction. Unfortunately, identifying and understanding the relative importance of these potential mechanisms is difficult with conventional cardiopulmonary exercise testing (CPET) as only VO_2 is directly measured.

We have developed a novel technique that combines exercise cardiovascular magnetic resonance (MR) with CPET (MR-CPET), allowing the simultaneous measurement of VO_2 and CO during exercise.[8,9] These data can then be used to calculate arteriovenous oxygen content gradient (ΔavO_2), a recognized marker of tissue oxygen extraction.[10] MR-CPET provides a comprehensive evaluation of the cardiopulmonary exercise response, affording a better understanding of exercise intolerance. In addition, MR-CPET also allows the accurate evaluation of biventricular volumes and function during exercise. These data can be useful in understanding CO augmentation in terms of both contractile and preload reserve.

The aim of this study was to use MR-CPET to investigate exercise capacity in patients hospitalized due to COVID-19 infection, with and without self-reported exercise intolerance, through comparison with a healthy control group.

METHODS

Study Population

Sixty subjects were prospectively recruited into this single-center prospective observational case-control study and split into 3 equally sized groups: (1) self-reported reduced exercise capacity following COVID-19 infection ($COVID_{reduced}$); (2) normal exercise capacity following COVID-19 infection ($COVID_{normal}$); and (3) age- and sex-matched normal controls. Patients who had recovered from COVID-19 were recruited from the Royal Free London NHS Foundation Trust COVID-19 follow-up clinic between January and May 2021. Patients in the post–COVID-19 groups

were matched for age, sex, and the presence of diabetes and hypertension. Inclusion criteria for patients following COVID-19 were: (1) previous hospitalization with COVID-19 diagnosed by positive combined oro/nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 by reverse-transcriptase-polymerase chain reaction; (2) age 18 to 80 years. Exclusion criteria were: (1) radiological evidence of residual lung parenchymal disease secondary to COVID-19; (2) troponin positivity during hospital admission; (3) admission to an intensive care unit for invasive ventilation; (4) diagnosis of pulmonary embolism during acute COVID-19 illness; (5) impaired left ventricular (LV) or right ventricular (RV) systolic function on resting cardiovascular magnetic resonance (CMR); (6) general contraindications to MR scanning; (7) pre-existing contraindications to performing exercise (eg, unstable symptoms including angina, exertional syncope); (8) previous known cardiovascular disease (including ischemic, nonischemic, and moderate to severe valvular disease); and (9) significant lung parenchymal disease that may confound CPET results, such as emphysema or interstitial lung disease (defined as >20% lung volume on computed tomography imaging).

We also recruited 20 uninfected age- and sex-matched healthy control subjects who had no history of COVID-19 and no history of cardiovascular disease, hypertension, or diabetes through advertisement by our institution. Fourteen (70%) control subjects underwent MR-CPET before the pandemic. The 6 postpandemic controls had not experienced any prior symptoms or previously been diagnosed with COVID-19.

The study was approved by national ethics committee (IRAS project ID 226101; REC reference 17/LO/1499, National Health Service Health Research Authority UK CRN 058274). All subjects provided written informed consent. The study data set, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request to the corresponding author, subject to institutional and ethical committee approvals.

Clinical Assessment

All patients underwent a patient symptom perception questionnaire, 6-minute walk test, blood tests, and spirometry. Patients gave an overall percentage score of how they felt at the time of MR-CPET study compared with premorbid baseline. Patient clinical histories, comorbidities, and in-patient blood test results were obtained from patient electronic records systems. Physician-determined severity of acute COVID-19 disease was defined by World Health Organization guidelines.[11]

MR-Augmented Cardiopulmonary Exercise Testing

Imaging was performed on a 1.5 Tesla MR scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) in a temperature-controlled suite. Full resuscitation facilities were available with peripheral venous access sited for emergency and ECG continuously monitored on the MR scanner. Systolic blood pressure was recorded at rest and peak using a MR-compatible blood pressure monitor (Expression MR400, Philips Healthcare, Best, The Netherlands).

MR Imaging Techniques (Real-Time Flow and Volume Imaging)

Before exercise, subjects underwent routine CMR with long- and short-axis cine imaging and myocardial native T1 and T2 mapping.[12,13] T1 mapping used the modified Look-Locker inversion recovery sequence after regional shimming with 5s(3s)3s sampling.[14] T2 mapping used single-shot T2-prepared images with varying T2 preparation.[15]

All exercise CMR was performed with real-time sequences and was acquired during free breathing. Aortic flow was measured using real-time phase-contrast MR at baseline and at peak exercise using a uniform-density golden-angle spiral sequence, with a compressive sensing reconstruction.[9,16] The following parameters were used: matrix=192×192, slice thickness=7 mm, repetition time/echo time=9.8/1.6 ms, flip angle=25°, velocity encoding=300 cm/s, temporal resolution=~41 ms, spatial resolution=2.3×2.3 mm, and acceleration factor=6. Real-time assessment of biventricular volumes was performed immediately after real-time flow acquisition at rest and at peak exercise using a 2-dimensional multislice, real-time, tiny golden-angle spiral compressive sensing balanced steady-state free precession sequence.[9,17] The following parameters were used: matrix=208×208, slice thickness=8 mm, repetition time/echo time=3.4/0.7 ms, flip angle=67°, temporal resolution=~31 ms, spatial resolution=1.7×1.7 mm, and acceleration factor=8. Up to 14 slices were used in each acquisition, with each slice being acquired over 2 R-R intervals.

Aortic flow and short-axis image data were reconstructed offline (MATLAB R2018a, MathWorks Inc, Natick, MA), using the Berkeley Advanced Reconstruction Toolbox.[18] Reconstructed images were exported as Digital Imaging and Communications in Medicine files and analyzed on reporting workstations.

Respiratory Gas Analysis

Breath-by-breath gas exchange analysis was performed using a commercial CPET system (Ultima, MedGraphics, St Paul, MN). The analyzer was placed

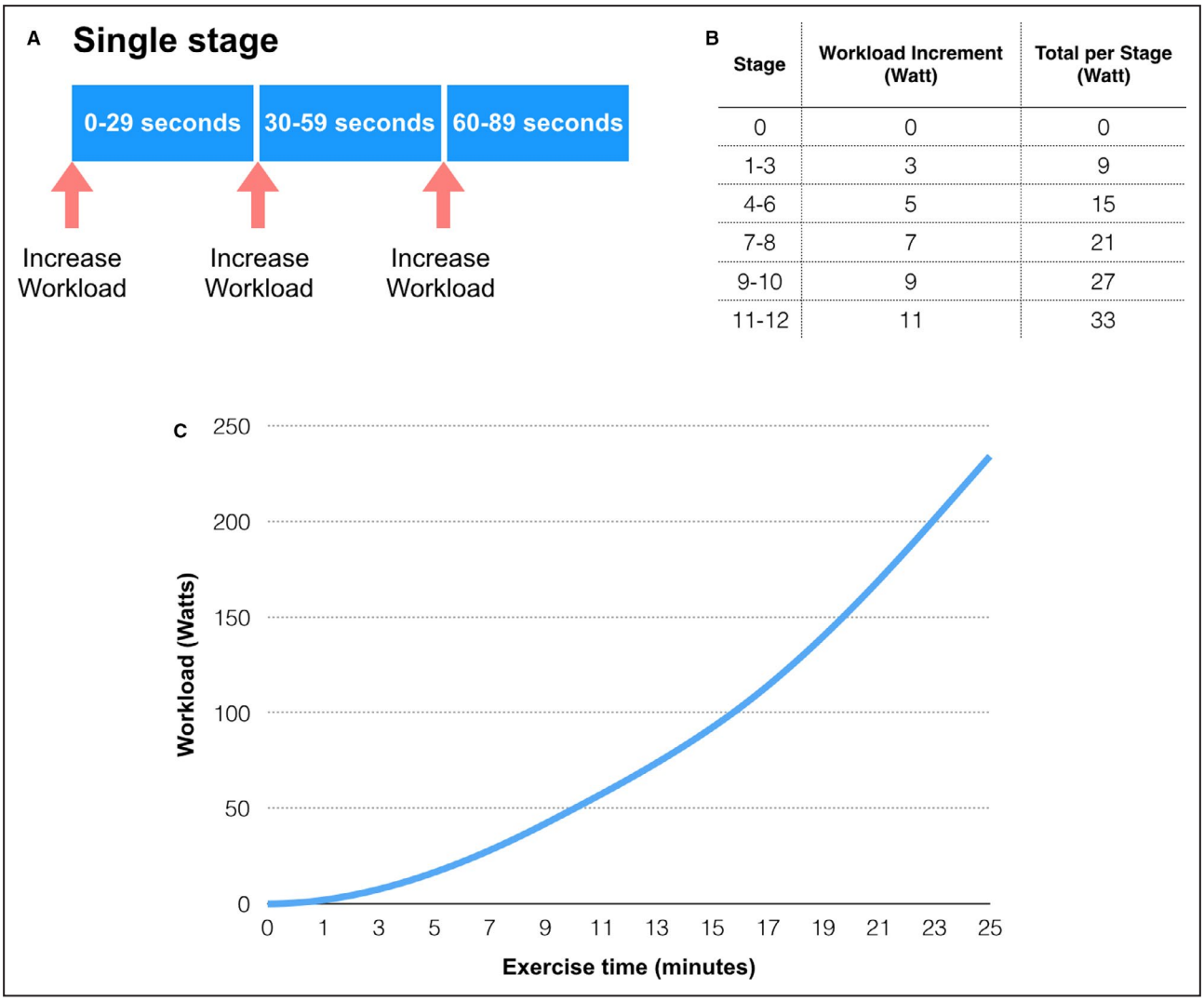
in the MR control room and attached to the face-mask (Hans Rudolph, Kansas City, KS) via bespoke MR-compatible sampling tubes passed through the waveguide. The sampling tubes were modified as previously described[8,9] and manufacturer-tested to meet all quality control standards. Gas and flow calibrations were performed before each test and at least 30 minutes after system initiation. All measurements were taken at body temperature and ambient pressure.

Exercise Protocol

Subjects exercised on a supine MR-compatible cycle ergometer (MR Cardiac Ergometer Pedal, Lode, Groningen, the Netherlands). Exercise workload (power measured in watts) was controlled by altering resistance depending on cadence. The exercise protocol (Figure 1) was followed until exhaustion (peak exercise) with MR measurements performed at rest and peak and VO_2 measured continuously.

Data Processing

All postprocessing of reconstructed images was performed using "in-house" plug-ins for OsiriX DICOM software version 9.0.1 (OsiriX Foundation, Geneva, Switzerland).[19–21] Aortic phase-contrast MR flow data was segmented using a semiautomatic method with manual operator correction. Stroke volume (SV) was calculated by integrating the flow curve across a single R-R interval; cardiac output was given by stroke volume×heart rate (CO=SV×HR). Biventricular endocardial borders were traced manually on short-axis images at end-diastole and end-systole, identified by visual assessment of the largest and smallest cavity



Stage	Workload Increment (Watt)	Total per Stage (Watt)
0	0	0
1-3	3	9
4-6	5	15
7-8	7	21
9-10	9	27
11-12	11	33

Figure 1. Magnetic resonance-cardiopulmonary exercise testing (MR-CPET) exercise protocol.
A, The protocol was split in 2-minute stages. During each stage, workload was increased at 0, 30, and 60 seconds. **B**, Workload increments by stage. Smaller increments at the start of the protocol were designed to ensure that subjects with significant exercise intolerance were able to complete at least 2 exercise stages. **C**, Cumulative workload as a function of time.

areas, respectively. Biventricular SV, ejection fraction, and mass were calculated as previously described, with papillary muscles and trabeculae excluded from the blood pool.[9] Postprocessing of SV data obtained by aortic phase-contrast MR flow imaging and by volumetry of cine images was performed in tandem to maintain internal consistency as suggested by Society for Cardiovascular Magnetic Resonance Task Force recommendations.[22] Biatrial areas were traced on a 4-chamber cine image at end-systole. Native myocardial T1 and T2 relaxation times were measured by drawing a single region of interest within the midportion of the interventricular septum on the midcavity short-axis maps.[13] All measurements were reported by an experienced clinical CMR specialist (D.K.) blinded to clinical information. All volumetric data and CO were indexed to body surface area and denoted by the suffix -i.

VO_2 and respiratory exchange ratio measurements were time registered to CMR data. The VO_2 was indexed to body weight and denoted by the prefix -i. Arteriovenous oxygen content gradient was calculated as $\Delta avO_2=VO_2/CO$ (using nonindexed data) at rest and peak exercise for all subjects.

Statistical Analysis

All statistical analysis was performed using R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Data were examined for normality using the Shapiro-Wilk normality test. Descriptive statistics were expressed as mean (±SD) for normally distributed data and median (interquartile range) for non-normally distributed data. Between-group differences in demographic data, clinical metrics, and MR-CPET metrics (at rest and exercise) were assessed using either 1-way ANOVA for normal data or the Kruskal-Wallis test for non-normal data. Post hoc comparisons were performed using pairwise *t* tests (normal data) and Mann-Whitney tests (non-normal data) with Benjamini Hochberg correction for multiple comparisons. When only comparing post–COVID-19 groups, *t* tests (normal data) and Mann-Whitney tests (non-normal data) were used. Sex distribution between the groups was assessed using the chi-squared test. Correlation between metrics corrected for diagnosis was computed using multilevel Spearman's rank partial correlation coefficient. A *P* value <0.05 was considered statistically significant.

RESULTS

Demographics and Clinical Data

There were no differences in age, sex, height, weight, or body surface area among the 3 groups and no differences in comorbidities between post–COVID-19 patient groups (Table 1). Clinical data for the post–COVID-19 groups are shown in Table 2. The only differences were significantly lower perceived functional recovery (70% of baseline [Interquartile range (IQR), 60–80] versus 98% [IQR, 90–100]; *P*<0.001) and 6-minute walk test (470±87meters versus 560±117 meters; *P*=0.009) in the $COVID_{reduced}$ group. There were no differences in any markers of disease severity between post–COVID-19 patient groups. There were also no significant differences in blood biomarkers at the time of MR-CPET between patient groups. However, there was a trend toward a greater length of time from discharge to MR-CPET in the $COVID_{normal}$ group (115 days [IQR, 96–151] versus 97 days [IQR, 80–116]; *P*=0.07).

There were no significant differences in spirometry metrics at the time of MR-CPET between the 2 post–COVID-19 patient groups. Two patients in the $COVID_{reduced}$ group and 4 patients in the $COVID_{normal}$ group had normal index chest radiographs. As per clinical patient follow-up protocol, they did not have follow-up chest imaging. The remaining 34(85%) patients had outpatient follow-up chest radiographs, all of which were normal.

Resting MR-CPET

Resting CMR metrics are shown in Table 3. The main differences in functional metrics between the 2 post-COVID-19 patient groups and controls were higher LV ejection fraction ($COVID_{reduced}$ 68%±7% versus

Table 1. Patient Characteristics

	Control	$COVID_{reduced}$	$COVID_{normal}$	*P* value
Age, y	51±4	52±14	52±8	0.98
Weight, kg	73±13	79±13	80±20	0.23
Height, m	1.7±0.1	1.7±0.1	1.7±0.1	0.87
BSA, m^2	1.8±0.2	1.9±0.2	1.9±0.3	0.19
Female, n (%)	12 (60)	11 (55)	11 (55)	>0.99
Diabetes, n (%)	…	1 (5)	1 (5)	>0.99
Hypertension, n (%)	…	6 (30)	3 (15)	0.45

Normally distributed data displayed as mean±SD. BSA indicates body surface area; $COVID_{normal}$, normal exercise capacity following COVID-19; and $COVID_{reduced}$, reduced exercise capacity following COVID-19.

Table 2. Clinical Data for Patient Groups

	$COVID_{reduced}$	$COVID_{normal}$	*P* value
Perception of recovery (% of normal)	70 (60–80)	98 (90–100)	<0.001*
6-min walk distance (m)	470±87	560±117	0.0089*
Duration from discharge to MR-CPET (d)	97 (80–116)	115 (96–151)	0.068
Severity of acute COVID-19 illness			
Length of admission (d)	3.5 (1.0–5.2)	4.0 (0.8–5.0)	0.87
Severity score	4.0 (2.0–4.0)	4.0 (2.0–4.0)	0.69
Peak D-dimer, ng/mL	576 (373–1160)	496 (463–1020)	0.91
Peak CRP, mg/L	64 (21–116)	45 (23–133)	0.95
Current investigations			
FEV_1 (% predicted)	97 (91–102)	93 (88–100)	0.49
FVC (% predicted)	88 (79–93)	80 (76–93)	0.39
Hemoglobin, g/L	141±13	137±16	0.42
Creatinine, µmol/L	73±13	67±15	0.16
CK, units/L	93 (71–110)	107 (73–157)	0.29
NT-proBNP, ng/L	49 (49–122)	49 (49–64)	0.38

Normally distributed data displayed as mean±SD and non-normally distributed data shown as median (interquartile range). CK indicates creatine kinase; $COVID_{normal}$, normal exercise capacity following COVID-19; $COVID_{reduced}$, reduced exercise capacity following COVID-19; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MR-CPET, magnetic resonance–augmented cardiopulmonary exercise test; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Significant difference between post-COVID-19 patient groups.

$COVID_{normal}$ 69%±6% versus controls 61%±7%; $P \leq 0.004$) and RV mass ($COVID_{reduced}$ 25±5 g versus $COVID_{normal}$ 27±5 g versus controls 21±6 g; $P \leq 0.02$). There was also higher native myocardial T1 in the $COVID_{normal}$ group versus controls ($COVID_{normal}$ 1016±25 ms versus controls 994±22ms; $P=0.04$). There were no significant group differences in systolic blood pressure , biventricular size, biatrial size, indexed SV, heart rate, indexed oxygen uptake (iVO_2), or ΔavO_2 at rest.

Exercise Feasibility

All subjects successfully completed the exercise protocol. No subjects required medical intervention. All subjects achieved maximal respiratory exchange ratio ≥1.0. Comparisons of exercise duration and peak workload are shown in Table 4. The $COVID_{reduced}$ group had the lowest peak workload, which was significantly different from controls ($COVID_{reduced}$ 79W [IQR, 65–100] versus controls 104W [IQR, 86–148]; $P=0.01$) and shortest exercise duration ($COVID_{reduced}$ 13.3±2.8 minutes versus controls 16.6±3.5 minutes; $P=0.008$). There were no differences in peak workload or exercise duration patients between patients with $COVID_{normal}$ and controls.

Exercise MR-CPET Metrics

MR-CPET metrics at peak exercise are shown in Table 4 and Figure 2. The $COVID_{reduced}$ group had the lowest peak iVO_2 (14.9 mL/min per kg [IQR, 13.1–16.2]), significantly different from healthy controls (22.3 mL/min/kg [16.9–27.6]; $P=0.003$) and patients with $COVID_{normal}$ (19.1 mL/min per kg [IQR, 15.4–23.7]; $P=0.04$). The $COVID_{reduced}$ group also had lower peak indexed cardiac output (COi) (4.7±1.2 L/min per m^2) compared with controls (6.0±1.2 L/min per m^2; $P=0.004$) and patients with $COVID_{normal}$ (5.7±1.5 L/min per m^2; $P=0.02$). Lower peak COi during exercise was associated with lower indexed SV in patients with $COVID_{reduced}$ (39±10 mL/min per m^2) compared with controls (48±10 mL/min per m^2; $P=0.02$). Patients with $COVID_{reduced}$ also had lower body surface area indexed LV end-diastolic volume than controls (52±11 mL/min per m^2 versus 62±13 mL/min per m^2; $P=0.02$) and a trend toward lower indexed RV end diastolic volume (52 mL/min per m^2 [IQR, 50–56] versus 59 mL/min per m^2 [53–66]; $P=0.1$). There were no differences in peak ΔavO_2, systolic blood pressure, heart rate, LV ejection fraction, or RV ejection fraction between groups.

Current Clinical Status and MR-CPET Metrics

Peak iVO_2 ($r=0.73$, $P<0.001$), COi ($r=0.41$, $P=0.008$), ΔavO_2 ($r=0.46$, $P=0.003$), and heart rate ($r=0.49$, $P=0.001$) all correlated with the 6-minute walk test after adjusting for diagnosis. There were no significant correlations between the 6-minute walk test and peak RV ejection fraction, LV ejection fraction, or indexed SV. There were also no significant correlations between predicted forced vital capacity or forced expiratory volume during the first second and any peak-exercise MR-CPET metrics.

Disease Severity and MR-CPET Metrics

There was no association between measures of acute COVID-19 illness severity (length of admission and disease severity score) and any peak exercise MR-CPET metrics. However, peak iVO_2 ($r=0.37$, $P=0.02$), COi ($r=0.37$, $P=0.02$) and indexed SV ($r=0.32$, $P<0.05$) all correlated with length of time from discharge to MR-CPET.

DISCUSSION

The COVID-19 pandemic has caused significant mortality and morbidity worldwide.[23] Following resolution

Table 3. Resting MR-CPET Data

Variable	Control	$COVID_{reduced}$	$COVID_{normal}$	*P* value
iVO_2, mL/min per kg	3.2±0.5	3.1±0.8	3.6±0.7	0.14
COi, L/min per m^2	2.4 (2.2–2.8)	2.5 (2.3–3.0)	2.9 (2.4–3.2)	0.14
avO_2, mlO_2/100 mL	5.2±1.0	4.8±1.2	5.1±0.9	0.44
SVi, mL/min per m^2	39±9	36±7	40±7	0.35
Heart rate, bpm	67±12	73±12	73±13	0.21
Systolic BP, mm Hg	124 (117–128)	128 (121–138)	120 (116–126)	0.24
RVEDVi, mL/m^2	65 (54–75)	59 (52–69)	64 (56–69)	0.52
RVESVi, mL/m^2	24 (21–30)	20 (18–30)	22 (20–28)	0.29
RVSVi, mL/m^2	38±9	37±7	40±8	0.48
LVEDVi, mL/m^2	64±15	56±11	59±10	0.13
LVESVi, mL/m^2	25±7	18±6†	19±4.6†	0.0026*
LVSVi, mL/m^2	39±9	37±7	40±7	0.55
LVEF (%)	61±7	68±7†	69±6†	<0.001*
RVEF (%)	58±7	62±8	63±6	0.087
Septal T2, ms	46 (44–46)	46 (44–47)	46 (45–48)	0.58
Septal T1, ms	994±22	1007±29	1016±25†	0.045*
LV mass, g/m^2	56±15	54±9	58±10	0.61
RV mass, g/m^2	21±6	25±5†	27±5†	0.003*
LA area, cm/m^2	11±2	10±2	11±2	0.14
RA area, cm/m^2	11 (9–12)	9 (8–11)	10 (8–11)	0.17

The *P* value is for the appropriate omnibus test. Normally distributed data displayed as mean±SD and non-normally distributed data shown as median (interquartile range). avO_2 indicates tissue oxygen extraction; BP, blood pressure; COi, cardiac output indexed to body surface area (BSA); $COVID_{normal}$, normal exercise capacity following COVID-19; $COVID_{reduced}$, reduced exercise capacity following COVID-19; iVO_2, oxygen consumption indexed to weight; LA, left atrial; LVEDVi, BSA indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, BSA indexed left ventricular end-systolic volume; LVSVi, BSA indexed left ventricular stroke volume; MR-CPET, magnetic resonance-cardiopulmonary exercise testing; RA, right atrial; RVEDVi, BSA indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, BSA indexed right ventricular end-systolic volume; RVSVi, BSA indexed right ventricular stroke volume; SVi, BSA indexed stoke volume.

*Significant *Pvalue for the omnibus test*.

†Significant difference between controls and indicated patient groups.

of acute infection, ongoing exercise intolerance and failure to return to functional baseline are commonly described.[2,3] However, many patients have no obvious causes to account for these symptoms.[7] We used MR-CPET to evaluate potential mechanisms of exercise limitation in patients previously hospitalized with COVID-19 and without obvious resting cardiopulmonary pathological sequelae. The main findings of this study were: (1) the $COVID_{reduced}$ patient group had significantly lower peak iVO_2 than the $COVID_{normal}$ group and healthy controls; (2) this was attributable to lower peak COi during exercise, resulting from a failure to augment SV; (3) there were no abnormalities in cardiac contractile reserve, lung function, or ΔavO_2 to account for lower peak iVO_2 in $COVID_{reduced}$ patients; and (4) the deleterious effect on exercise capacity was unrelated to acute COVID-19 illness severity and lessened over time.

Peak VO_2 is an objective marker of exercise capacity that is determined by lung capacity, cardiac function, and peripheral tissue oxygen extraction. Studies have demonstrated reduced peak VO_2 in patients who have recovered from acute COVID-19 infection.[2,24] Although residual cardiovascular and pulmonary damage could explain these findings,[3,4] our study was designed to investigate exercise intolerance in patients without immediately attributable causes. Thus, we hoped to identify "subclinical" pathophysiology that might explain decreased exercise capacity in $COVID_{reduced}$ patients.

We demonstrated no differences in spirometry metrics between the 2 post–COVID-19 patient groups, implying that persistent lung damage was not the cause of exercise limitation. We also found no difference in peak ΔavO_2 between any of the groups, suggesting that skeletal muscle function was normal in our patients following COVID-19. This contrasts with a recent invasive CPET study that demonstrated impaired ΔavO_2 in a group of patients who were exercise intolerant following COVID-19.[24] However, there were some notable differences between the studied cohorts. First, most patients in the invasive CPET study had not been hospitalized during their acute COVID-19 illness. Second, the time from illness to examination was markedly longer in the invasive CPET study (≈11 months) compared with our medium-term follow-up cohort (≈3 months). Nevertheless, the differences suggest heterogeneity

Table 4. Exercise MR-CPET Data

Variable	Control	$COVID_{reduced}$	$COVID_{normal}$	*P* value
Metrics of exercise performance				
Exercise duration (min)	16.6±3.5	13.3±2.8†	15.1±3.8	0.01*
Peak workload (W)	104 (86–148)	79 (65–100)†	104 (71–134)	0.017*
Maximum RER	1.6±0.2	1.4±0.2†	1.5±0.2	0.043*
MR-CPET metrics				
iVO_2, mL/min per kg	22.3 (16.9–27.6)	14.9 (13.1–16.2)†, ‡	19.1 (15.4–23.7)	0.0037*
COi, L/min per m^2	6.0±1.2	4.7±1.2†, ‡	5.7±1.5	0.0041*
avO_2, mlO_2/100 mL	14.8±3.9	13.5±3.4	13.8±2.8	0.46
SVi, mL/min per m^2	47.7±10.4	39.1±10.0†	43.2±7.4	0.02*
Heart rate, bpm	130±22	122±22	132±24	0.35
Systolic BP, mm Hg	145±22	150±26	154±16	0.37
RVEDVi, mL/m^2	59 (53–66)	52 (50–56)	59 (48–63)	0.098
LVEDVi, mL/m^2	62±13	52±11†	56±11	0.023*
LVEF (%)	76±8	74±10	78±8	0.31
RVEF (%)	76 (69–84)	75 (70–79)	76 (72–81)	0.55

The *P* value is for the appropriate omnibus test. Normally distributed data displayed as mean±SD and non-normally distributed data shown as median (interquartile range). avO_2 indicates tissue oxygen extraction; BP, blood pressure; COi, cardiac output indexed to body surface area (BSA); $COVID_{normal}$, normal exercise capacity following COVID-19; $COVID_{reduced}$, reduced exercise capacity following COVID-19; iVO_2, oxygen consumption indexed to weight; LVEDVi, BSA indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR-CPET, magnetic resonance-cardiopulmonary exercise testing; RER, Respiratory Exchange Ratio; RVEDVi, BSA indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; and SVi, BSA indexed stoke volume.

*Significant *P* value for the omnibus test.

†Significant difference compared with controls.

‡Significant difference between COVID patient groups.

in the pathophysiology of persistent exercise intolerance following COVID-19. This is in keeping with the finding of different exercise phenotypes in patients with postviral chronic fatigue syndrome, characterized as either low flow (with underlying low biventricular filling) or high flow (associated with impaired systemic oxygen extraction).[25] Finally, while both studies use a cycle ergometer, MR-CPET is performed supine rather than conventional upright cycling. This affects exercise physiology, such as aerobic work efficiency and muscle deoxygenation response,[26,27] and may account for some differences between study findings.

In our study, reduced iVO_2 in $COVID_{reduced}$ patients appeared to be attributable to a failure to augment CO. This was caused by an inability to increase SV during exercise, with no evidence of chronotropic incompetence. The most obvious reason for reduced SV augmentation is impaired contractile reserve. This is particularly pertinent considering the high prevalence of post–COVID-19 CMR abnormalities, including myocarditis.[28] However, we excluded patients with evidence of troponin positivity during their hospital admission. It is worth noting that both patient groups had the higher resting LV ejection fraction, RV mass, and native myocardial T1. While these parameters were in keeping with reference ranges in the general population,[4,29] the differences versus the controls indicate that the patient groups did not have completely "normal" hearts. This might represent the background health status of these previously hospitalized patients and could possibly be suggestive of subclinical cardiovascular disease. Nevertheless, peak exercise biventricular ejection fractions were the same in all groups, and there were no differences in RV mass and T1 between the patients with and without exercise intolerance. These findings go against the idea of contractile dysfunction being the cause of reduced CO augmentation in $COVID_{reduced}$ patients. Another reason for failure to augment SV on exertion could be diastolic dysfunction, but the similar left atrial sizes and LV masses among all the groups make this less likely. In the absence of abnormalities of systolic or diastolic function, we propose that inadequate preload could be a remaining cause of reduced SV augmentation to consider in the $COVID_{reduced}$ patient group.

Factors that control ventricular filling (not directly assessed in this study) include blood volume and venous compliance. Indeed, blood volume is one of the most important factors in maintaining ventricular filling. Blood volume depletion is known to reduce exercise capacity,[30] is depleted in postviral chronic fatigue syndrome, and correlates with exercise symptoms.[31,32] Furthermore, volume expansion in these patients results in improved exercise tolerance.[30] It is possible that similar mechanisms could occur in some patients following COVID-19, reducing ventricular filling during exercise and contributing to exercise intolerance. Similar mechanistic origins of disease would perhaps be

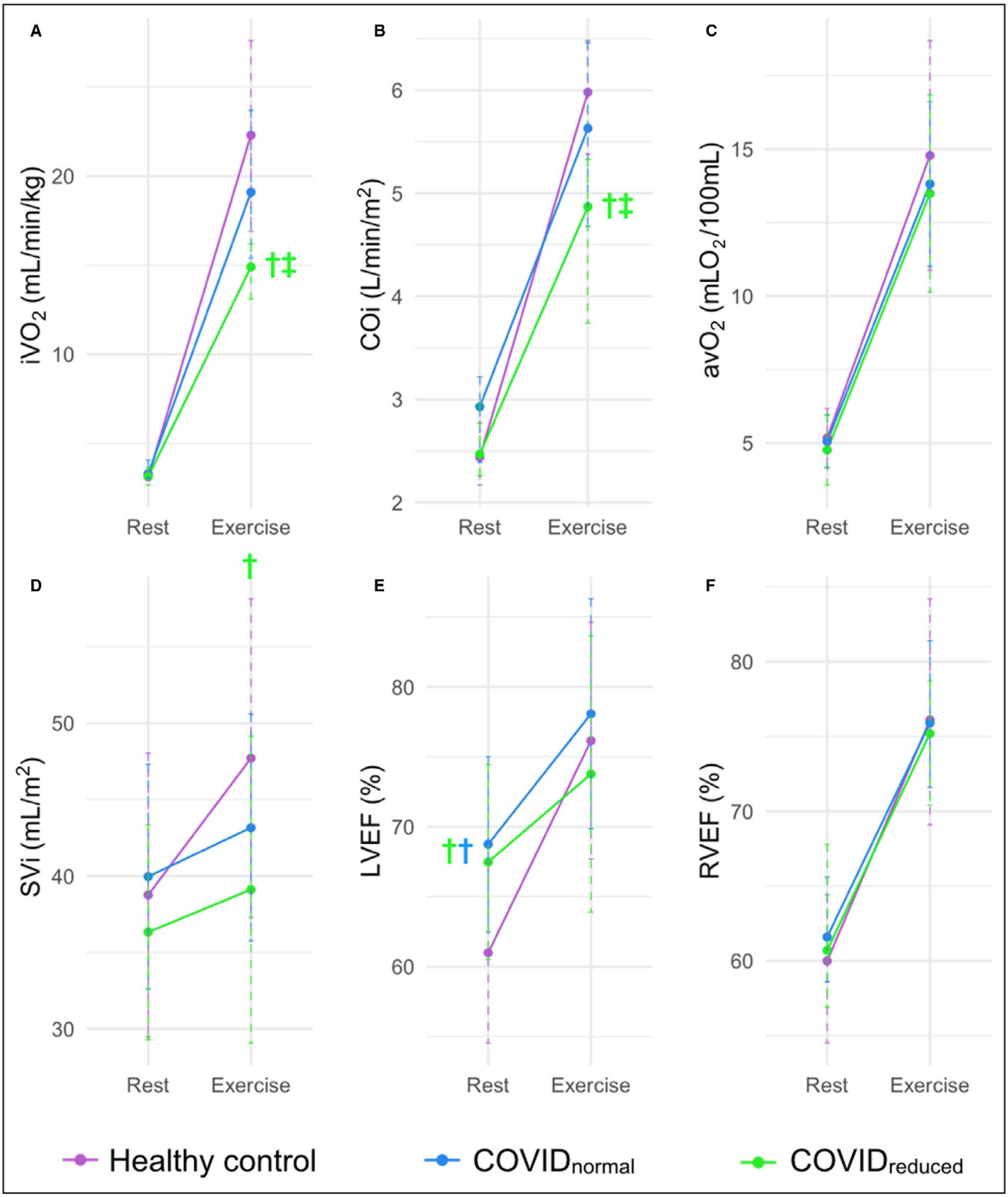


Figure 2. MR-CPET metrics at rest and peak exercise for each subject group.
A, Oxygen consumption indexed to weight (iVO_2). **B**, Cardiac output indexed to body surface area (COi). **C**, Arteriovenous oxygen gradient (ΔavO_2). **D**, Stroke volume indexed to body surface area (SVi). **E**, Left ventricular ejection fraction (LVEF). **F**, Right ventricular ejection fraction (RVEF). †Significant difference between the color-coded group and controls. ‡Significant difference between COVID patient groups. $COVID_{normal}$ indicates normal exercise capacity following COVID-19; and $COVID_{reduced}$, reduced exercise capacity following COVID-19.

unsurprising given the symptom overlap between postviral chronic fatigue syndrome and patients following COVID-19. Possible causes of reduced blood volume following COVID-19 that could be evaluated in future studies include detraining after severe illness, abnormal renal regulation of fluid balance, and reduced fluid or salt intake.[33,34] Although these causes require further investigation, they do raise the possibility of interventions tailored to volume expansion, such as increased hydration and salt intake. The other important contributor to preload is venous compliance, which controls the proportion of the total blood volume that is "stressed." It is stressed that blood volume that directly contributes to preload and dynamic reduction of venous compliance is required to increase preload during exercise. Venous compliance is controlled by the autonomic system, and there is some evidence of dysautonomia in patients with postviral chronic fatigue syndrome[34] along with small studies demonstrating dysautonomia in patients following COVID-19.[35,36] Thus, an inability to dynamically reduce compliance may contribute to reduced exercise capacity in the $COVID_{reduced}$ group and also requires further investigation.

Irrespective of the cause of reduced SV and CO at peak exercise, we did show that exercise capacity appears to improve with time since discharge. This suggests that reduced exercise capacity following COVID-19 is not permanent and that a return to baseline is possible. Of course, this requires long-term surveillance, as well as identification of interventions that may hasten recovery. In this regard, future work should include the longitudinal serial assessment of exercise capacity over a sufficient time period to ensure adequate time for recovery (eg, at 1 year). Interestingly, we also showed no association between exercise capacity and disease severity, which is consistent with other studies of patients with previous COVID-19 infection.[37] This strengthens the idea that exercise intolerance is not simply the result of residual organ damage but a specific response to COVID-19 infection.

One of the unique aspects of this study is the use of MR-CPET. This technique enables simultaneous quantification of peak VO_2 and CO, with subsequent calculation of ΔavO_2, but is dependent on real-time MR sequences. These can be challenging to use and require optimization to ensure robustness, particularly during exercise. We have previously shown that one of the most important factors in determining the reproducibility of real-time MR is spatial and temporal resolution.[38] Thus, we used highly accelerated spiral acquisitions, reconstructed using compressed sensing. These techniques provide spatial and temporal resolution only slightly lower than clinical sequences. We have previously validated accelerated real-time spiral sequences with compressed sensing reconstruction for assessment of aortic flow and ventricular volumes.[16,17] Unfortunately, validation at peak exercise with conventional gated breath-hold or respiratory averaged MR is not possible. It should also be noted that these techniques are not widely available and can be challenging to use, meaning that MR-CPET cannot be considered a clinical tool at the moment. Nevertheless, MR-CPET does allow more sophisticated investigation of pathophysiology enabling generation of important new hypotheses. Furthermore, high-resolution real-time sequences are starting to become more clinically available,[39] opening the possibility of MR-CPET being used as a clinical test. Of course, this will require further validation both of real-time sequences (at peak exercise) and MR-CPET in general. Simultaneous right heart catheterization and CPET (invasive CPET) is the reference standard direct method of measuring of ΔavO_2.[24,30] Furthermore, invasive CPET can be performed using conventional metabolic carts and upright exercise ergometers, and allows traditional catheter-based estimation of CO. We have previously shown that VO_2 measured during MR-CPET correlates well with VO_2 measured during conventional CPET.[8] In addition, resting CO by phase-contrast MR correlates well with CO measured invasively.[40] However, MR-CPET measurements of exercise CO and ΔavO_2 have not been directly compared with invasive CPET. This is mainly attributable to the significant difficulties in performing simultaneous MR and invasive CPET. Nevertheless, validating our novel technique is desirable, and future work should investigate a way of overcoming the logistical barriers to a direct comparison.

There are limitations of the study to consider. The $COVID_{reduced}$ and $COVID_{normal}$ groups, but not the control group, were matched for hypertension and diabetes. While this is an important limitation, it does not account for the differences in MR-CPET metrics between the 2 post–COVID-19 patient groups given their matching for these comorbidities. Furthermore, there were no differences in peak iVO_2 and peak COi between the $COVID_{normal}$ group and healthy controls. These results suggest that the absence of comorbidity matching in the control group did not significantly affect the results. As patients with significant cardiac and respiratory diseases were excluded, we only matched post–COVID-19 patient groups by age, sex, hypertension, and diabetes. We believe that this covers most confounders of exercise capacity, but in future studies with larger recruitment, it may be beneficial to more extensively match groups. Neither of the patient groups were matched for pre–COVID-19 exercise history because of the difficulty in ascertaining accurate exercise histories. Future studies may be able to overcome this problem by excluding subjects who are unable to provide an accurate exercise history, although this does risk introducing a significant selection bias. We did not have spirometry data for our healthy control group to compare against patient groups. However, this cohort was particularly advantageous as most data were

acquired before the pandemic and, therefore, would not have been confounded by prior COVID-19 infection. We have presented CMR-derived data of left atrial size and LV mass but no specific measures of diastolic function, which should also be evaluated in future work. Further studies should also include the assessment of exercise capacity in response to intravenous fluid challenge, as we propose blood volume depletion as a potential cause of impaired SV augmentation.

Our MR-CPET study emphasizes the importance of SV augmentation in the normal response to exercise. There were no differences in contractile reserve, left atrial size or LV mass (suggestive of diastolic impairment), or peak afterload that could explain reduced SV augmentation in $COVID_{reduced}$ patients. Therefore, we propose that inadequate preload could be a possible mechanism of reduced SV augmentation and, consequently, of exercise intolerance in these patients. However, this is a hypothesis of exclusion, and larger, more statistically powered studies are required to fully understand the origin of exercise intolerance in these patients. Our data show no relationship between disease severity and peak MR-CPET metrics and, reassuringly, that abnormalities in peak MR-CPET metrics may improve with time from the acute illness. We believe that the comprehensive evaluation of unexplained dyspnea and exercise intolerance is pivotal to help correctly identify potential therapeutic targets in these patients.

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