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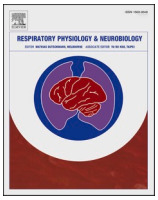

Short communication

Exercise intolerance associated with impaired oxygen extraction in patients with long COVID

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ABSTRACT

Objective: Chronic mental and physical fatigue and post-exertional malaise are the more debilitating symptoms of long COVID-19. The study objective was to explore factors contributing to exercise intolerance in long COVID-19 to guide development of new therapies. Exercise capacity data of patients referred for a cardiopulmonary exercise test (CPET) and included in a COVID-19 Survivorship Registry at one urban health center were retrospectively analyzed. *Results*:
Most subjects did not meet normative criteria for a maximal test, consistent with suboptimal effort and early exercise termination. Mean O_2 pulse peak % predicted (of 79 ± 12.9) was reduced, supporting impaired energy metabolism as a mechanism of exercise intolerance in long COVID, n = 59. We further identified blunted rise in heart rate peak during maximal CPET. Our preliminary analyses support therapies that optimize bioenergetics and improve oxygen utilization for treating long COVID-19.

1. Introduction

Long COVID-19 occurs in approximately 10 – 20% of survivors of COVID-19, representing about 10 – 20 million global long-term cases (Vehar et al., 2021; Wise, 2021). It is characterized by persistent, multi-organ symptoms beyond 3 months from onset of acute illness. (Soriano et al., 2021) Chronic fatigue, exercise intolerance, post-exertional malaise (PEM), and orthostatic intolerance are some of the more debilitating symptoms of long COVID-19. Exercise intolerance is defined as the "inability to exercise to near age-appropriate maximum heart rate due to exacerbation of symptoms".(Leddy et al., 2021),p.3 PEM is defined as "inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, tendency for symptoms to worsen, or prolonged exacerbation of patient's baseline symptoms after physical, cognitive, and orthostatic stress" (Jason et al., 2021), p.238 PEM symptom exacerbation can be immediate after exertion or can be delayed for 24–72 h.

Underlying mechanisms of exercise intolerance in the chronic or "long-hauler" phase of COVID-19 are likely multifactorial. Impaired mitochondrial function (regulation of energy metabolism) and oxygen metabolic homeostasis (e.g., oxygen transportation and sensing) may be a significant contributing factors to fatigue and impaired exercise tolerance in long COVID (Astin et al., 2023). Impaired autonomic nervous system (ANS) function can result in dysregulated heart rate, blood pressure, respiratory, gastrointestinal, thermoregulatory, and bladder functions. Exercise intolerance may be associated with blunted or

Abbreviations: AT, Anaerobic threshold; COVID-19, Coronavirus disease 2019; CPET, Cardiopulmonary exercise testing; $FEV_{1,}$, Forced expiratory volume in one second; FVC, Forced vital capacity; HR, Heart rate; HRR, Heart rate reserve; IQR, Interquartile range; ICU, Intensive care unit; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome; MET, Metabolic equivalent; PEF, Peak expiratory flow; PEM, Post-exertional malaise; RER, Respiratory exchange ratio; RPP, Rate-pressure product; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, Standard deviation; V_E/V_{Co2}, Ventilatory equivalent for CO2; $VO_{2,}$, Oxygen consumption.

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decreased age-predicted maximal heart rate (HR), also called chronotropic intolerance (CI). CI is diagnosed by inability to meet 80% of age-derived HR_{peak} during a noninvasive maximal cardiopulmonary exercise testing (CPET) (Jimeno-Almazán et al., 2021). The aim of our observational, retrospective study was to explore factors contributing to exercise intolerance in long COVID-19 to guide development of new therapies.

2. Methods

Patients recovered from positive, acute COVID-19 infection and referred for cardiopulmonary exercise testing (CPET) at an urban Ambulatory Care Center, between March and August 2020, were included in a COVID-19 Survivorship Registry. Inclusion criteria were at least 21 years of age with positive COVID-19 infection in electronic medical record. Participants' exercise capacity was compared to reference normative data. Statistical differences in the cohort were calculated between patient sub-groups based on standard % predicted peak oxygen

Table 1
Differences based on VO_2 Maximum Exercise Capacity Criterion.

	Total Sample	VO_2 peak > 84% pred	VO_2 peak ≤ 84% pred	p-value
n (%)	59	35 (59)	24 (41)	
Age, years	53.9 (15)	54.7 (15.8)	52.7 (14)	0.61
Sex (%)				0.371
Male	34 (57.6)	18 (51.4)	16 (66.7)	
Female	25 (42.4)	17 (48.6)	8 (33.3)	
Race (%)				0.183
White	29 (50.0)	21 (61.8)	8 (33.3)	
African American	10 (17.2)	5 (14.7)	5 (20.8)	
Asian	5 (8.6)	1 (2.9)	4 (16.7)	
Chinese	2 (3.4)	2 (5.9)	0 (0.0)	
Filipino	4 (6.9)	2 (5.9)	2 (8.3)	
Latino	6 (10.3)	2 (5.9)	4 (16.7)	
Other	2 (3.4)	1 (2.9)	1 (4.2)	
Weight loss post-COVID-19 (lbs.)	14.4 (14.3)	17.4 (14.4)	15 (14.5)	0.457
Hospitalized (%)	32 (56.1)	18 (52.9)	14 (60.9)	0.749
Inpatient rehabilitation (%)	21 (36.8)	12 (35.3)	9 (39.1)	0.988
ICU (%)	23 (41.8)	12 (37.5)	11 (47.8)	0.625
Mechanical ventilation (%)	20 (36.4)	11 (34.4)	9 (39.1)	0.938
Days from hospital discharge	69 (57–143)	64 (55.2–98)	125 (69–146)	0.211
Days from positive COVID-19 test diagnosis	167 (68.8)	159.3 (68.1)	177.8 (70)	0.332
Length of stay, days	38.1 (26.9)	32.8 (23.2)	44.9 (30.7)	0.249
Days in ICU	13.5 (10.3)	12.9 (11.4)	16 (5.7)	0.614
FVC % pred	74 (64–90)	80 (69–94)	63.5 (54.2–81.5)	0.003
FEV_1% pred	82.2 (18.5)	88.1 (15.9)	73.6 (18.8)	0.004
FEV_1/FVC	85.2 (8)	84.5 (7.7)	86.3 (8.4)	0.407
PEF % pred	95 (83.5–106.5)	102 (91–110)	85 (77–95)	0.001
FEF 25–75%	100 (82.5–118.5)	102 (85.5–118.5)	96.5 (80.2–117)	0.436
Performance				
V_{O2peak} (ml/kg/min)	21.8 (6.1)	24.3 (5.2)	18.2 (5.6)	< 0.001
V_{O2peak} (ml/kg/min) % pred	89.2 (22.2)	104.2 (12.5)	67.4 (13.1)	< 0.001
V_{O2} AT (ml/kg/min)	12.2 (3)	13.3 (2.7)	10.6 (2.7)	< 0.001
Anaerobic threshold (AT/predicted VO_2 max x 100)	57.4 (8.8)	55.7 (8.1)	50.0 (9.2)	0.069
Actual MET	6.2 (1.7)	7 (1.5)	5.2 (1.6)	< 0.001
MET pred	7.7 (2.8)	8.6 (2.4)	6.5 (2.8)	0.004
Test Duration (n = 38)	7.44 (1.92)	7.88 (1.84)	6.41 (1.76)	0.031
Test Duration % pred (n = 38)	79.60 (22.26)	87.85 (20.55)	60.10 (11.55)	< 0.001
Circulation				
Peak systolic	162.4 (24.2)	168.7 (23.4)	153.2 (22.7)	0.017
Peak diastolic	80 (70–80)	80 (70–80)	70 (66–80)	0.242
HR reserve (beats/min)	16 (3.5–27.5)	6 (0–17.5)	27 (17–44.5)	< 0.001
HR peak	149.2 (23.1)	156.7 (19)	138.3 (24.5)	0.004
HR % pred	89.8 (11.4)	94.9 (9.2)	82.3 (10.4)	< 0.001
HR AT	105.9 (14.9)	107.8 (13.4)	103.2 (16.7)	0.267
HR peak % pred	71.5 (8.3)	69.1 (7.5)	75 (8.2)	0.007
Cardiovascular Function				
Peak V_{O2}/HR	11.6 (9.9–13.7)	12.4 (10.9–14.4)	10.7 (9.1–11.9)	0.002
O_2 pulse peak % pred	79 (12.9)	78.6 (13.7)	79.5 (11.7)	0.772
V_{O2}/HR AT	9.4 (2.7)	10.3 (2.7)	8.2 (2.2)	0.002
V_{O2}/HR % pred	99.3 (21)	110.6 (13.5)	82.8 (19)	< 0.001
Rate-pressure product (RPP)	22,700 (18,186–26767.5)	23,940 (22,176–28730)	18,144 (15,865–23430)	< 0.001
Ventilation				
Peak V_E (L/min)	71.5 (24.4)	80.2 (22)	58.8 (22.4)	< 0.001
V_E % pred (SD)	81 (21.3)	87.1 (18.6)	72 (22.3)	0.009
V_E reserve (range)	18 (4–29.5)	17 (0–24.5)	23 (5.8–37.2)	0.107
Gas exchange				
V_E/V_{Co2} AT	31.8 (29.1–35.6)	31.6 (28.6–34.6)	32.5 (29.9–38.7)	0.208
RER peak	1.11 (0.12)	1.13 (0.10)	1.08 (0.13)	0.099
Sp_{O2} minimum	95 (94–97)	95 (94–97)	95 (92.8–98)	0.938

Note. AT: at threshold. HR: heart rate. Lbs: pounds. FVC: forced vital capacity. Min: minutes. O_2: oxygen; PEF: peak expiratory flow. pred: predicted. RER: respiratory exchange ratio at end of test. RPP: rate-pressure product. VE: minute ventilation. V_E/V_{Co2} AT: ventilatory equivalent for carbon dioxide. V_{O2}: oxygen uptake; V_{O2}/HR: oxygen pulse. V_E/V_{CO2} ratio: ventilatory equivalent for carbon dioxide.

consumption ($VO_{2\ peak}$). To diagnose CI, we analyzed a subgroup of patients who completed a maximal CPET (defined by an $RER_{peak} > 1.05$ (Radtke et al., 2019)) and who were not admitted to ICU (Davenport et al., 2019). RER is VCO_2/VO_2 (ATS/ACCP, 2003). We also compared subgroups based on gender, since long COVID-19 may be more prevalent in women (Torjesen, 2021).

We evaluated lung function with spirometry and exercise capacity using gold standard CPET on a treadmill (Vyaire Medical, Mettawa, IL) with the Bruce protocol (Myers et al., 1991). In particular, we used the 2012 European Respiratory Society Global Lung Function Initiative's (GLI) prediction equations, with age- and gender-dependent lower limits of normal and validity across different ethnic groups, to calculate lung volume, diffusion, spirometry, and exercise capacity values.(Quanjer et al., 2012)

Past medical history data were collected, including hospital length of stay, need for intensive care unit (ICU), and mechanical ventilation. Quantitative demographic and clinical variables were evaluated using Student's t-test or a Wilcoxon Rank Sum test, depending on whether the given variable was normally distributed. The Shapiro-Wilk test was used to examine the normality of each quantitative variable. Pearson's Chi-square test was used to assess qualitative variables such as gender and race. Statistical significance was considered as a p-value of < 0.05. The statistical analysis was conducted with R-3.5.1.[a].

Normal exercise capacity was defined as $VO_{2peak} > 84\%$ predicted, (ATS/ACCP, 2003) and $> 80\%$ predicted for other exercise parameters (ATS/ACCP, 2003) We hypothesized that exercise intolerance was associated with impaired oxygen extraction, autonomic dysfunction, and deconditioning in patients with long COVID-19.

3. Results

We collected CPET data on 59 long COVID-19 participants (34 men, 58%) with a mean (SD) age of 53.9 years (15.0). Average (SD) days after positive infection diagnosis was 167 (68.8). 56% of participants had been hospitalized with acute COVID-19, 42% of whom required ICU. 87% of patients in ICU required mechanical ventilation. 82.6% of patients admitted to ICU received inpatient pulmonary rehabilitation compared with only 6.2% of patients hospitalized without ICU stay ($p < 0.001$). Race was a significant social determinant of whether a patient was admitted to the ICU ($p = 0.024$). Except for forced vital capacity (FVC), which was an average of 74% predicted (range: 64–90), mean spirometry values were normal in our sample.

Mean (SD) O_2 pulse peak % predicted was 79 (12.9) (Table 1). Test duration was 79.6 (22.3) % predicted (Table 1). Mean % predicted HR_{peak} was $\leq 75\%$. 24 participants (41%) had reduced exercise capacity, defined by a VO_2 peak $\leq 84\%$ (ATS/ACCP, 2003). Mean V_{O2} peak was 89.2% (SD = 22.2%). 18 participants (30.5%) showed high (≥ 34) V_E/Vco_2 slope.

Reduced exercise capacity defined as VO_2 peak $\leq 84\%$ pred. Normal exercise capacity defined as VO_2 peak $> 84\%$ predicted.

Table 2
Differences based on VO_2 Maximum in Patients with a Maximal CPET.

	Total Sample	VO_2 peak > 84% pred	VO_2 peak ≤ 84% predicted	p-value
n (%)	19	13	6	
Age, years	54 (15.9)	52 (18.7)	58.3 (6.2)	0.287
Sex (%)				0.735
Male	9 (47.4)	7 (53.8)	2 (33.3)	
Female	10 (52.6)	6 (46.2)	4 (66.7)	
Race (%)				0.105
FVC % pred	79.8 (15.8)	85.6 (12.9)	67.2 (14.8)	0.028
FEV_1% pred	85.4 (14)	91 (9.6)	73.3 (15.1)	0.035
FEV_1/FVC	84.3 (6.8)	83.5 (6.1)	85.8 (8.5)	0.57
PEF % pred	98 (17.5)	104.4 (16.8)	84.2 (9.3)	0.004
Performance				
V_{O2peak} (ml/kg/min)	22.6 (7.2)	25.4 (6.2)	16.4 (5.4)	0.008
V_{O2peak} (ml/kg/min) % pred	100 (78–106)	105 (100–108)	72 (58–75.5)	< 0.001
V_{O2} AT (ml/kg/min)	12.1 (3.8)	13.5 (3.4)	9.1 (2.8)	0.012
VO2 AT/peak % pred	54.5 (9.8)	53.5 (9.3)	56.8 (11.2)	0.500
Actual MET	6.4 (2.1)	7.2 (1.8)	4.7 (1.5)	0.011
MET pred	7.9 (3.4)	8.9 (2.9)	5.7 (3.5)	0.083
Test Duration (n = 15)	7.8 (2.3)	8.3 (2.0)	4.5 (0.0)	0.019
Test Duration % pred (n = 15)	86.5 (23.4)	91.4 (20.9)	54.8 (9.9)	0.033
Circulation				
Peak systolic	154.2 (22.8)	159.7 (24.3)	140 (9.4)	0.025
Peak diastolic	71 (70–80)	72 (70–80)	70 (70–72)	0.644
HR reserve (beats/min)	16 (2–25.5)	5 (0–16)	33 (25.2–46.8)	0.002
HR peak	150.3 (24.3)	161.5 (19.7)	126 (12.9)	< 0.001
HR % pred	90.4 (10.9)	96.1 (6.7)	78.2 (7.4)	< 0.001
HR AT	102.6 (13.6)	105.2 (14.4)	97 (10.5)	0.183
HR peak % pred	69 (7.7)	65.5 (6.3)	76.7 (4)	< 0.001
Cardiovascular Function				
Peak V_{O2}/HR	11.9 (10.1–13.7)	11.9 (10.7–13.8)	11.2 (9.7–13.3)	0.483
O_2 pulse peak % pred	77.4 (18.9)	79.9 (19.6)	72 (17.4)	0.396
V_{O2}/HR AT	9.9 (8.8–11.4)	11.1 (9.3–11.9)	9.4 (6.8–9.9)	0.105
V_{O2}/HR % pred	100.9 (15.6)	107.1 (10.7)	87.7 (17.1)	0.039
Rate-pressure product (RPP)	22,764 (17,503.5–27654)	25,110 (22,680–29070)	17,082 (14,850–17290)	0.008
Ventilation				
Peak V_E (L/min)	80.2 (24.2)	87.3 (25.1)	64.7 (13.3)	0.02
V_E % pred	86 (19.5)	88.5 (20.2)	80.5 (18.1)	0.405
V_E reserve (L/min)	14 (2–24.5)	17 (0–24)	10.5 (4–26)	0.86
Gas exchange				
V_E/V_{Co2} AT	33.4 (7.8)	31.3 (6.8)	38 (8.4)	0.122
RER peak	1.2 (0.1)	1.2 (0.1)	1.1 (0.03)	0.004

Note. AT: Anaerobic threshold. HR: heart rate. Lbs: pounds. FVC: forced vital capacity. Min: minutes. O_2: oxygen; pred: predicted. PEF: peak expiratory flow. RER: respiratory exchange ratio at end of test. RPP: rate-pressure product. VE: minute ventilation. V_E/V_{Co2} AT: ventilatory equivalent for carbon dioxide. V_{O2}: oxygen uptake; V_{O2}/HR: oxygen pulse. V_E/V_{CO2} ratio: ventilatory equivalent for carbon dioxide.

Only 19 *non-ICU participants* completed a maximal CPET (Table 2). Mean (SD) HR_{peak} was 69 (7.7) % predicted in this subsample (Table 2), indicating blunted rise in HR (CI, i.e., inability to meet 80% of age derived HR_{peak}) during a maximal CPET (n = 19).(Jimeno-Almazán et al., 2021) In participants who achieved peak volume of oxygen consumed (VO_2)> 84%, mean HR peak % predicted was 65.5%, significantly below normative values.

Reduced exercise capacity defined as VO_2 peak ≤ 84% pred. Normal exercise capacity defined as VO_2 peak > 84% predicted.

Analyzing by sex, only women with reduced exercise capacity (VO_2 peak ≤84% pred) had higher mean V_E/Vco_2 slope of 38.8 at the anaerobic threshold (p = 0.049) compared with women demonstrating normal exercise capacity, which may reflect hyperventilation and ventilatory inefficiency (n = 25). In women only, mean (SD) peak respiratory exchange ratio (RER_{peak}) – the ratio of carbon dioxide metabolic production to oxygen uptake – of 1.0 (0.1) was reduced in the reduced exercise capacity subgroup compared with 1.1 (0.1) in normal exercise capacity subgroup, indicating sub-maximal effort and exertion intolerance (p = 0.038).(ATS/ACCP, 2003; Kim et al., 2016) In contrast to women, reduced exercise capacity was associated with worse pulmonary function values (FVC % pred, p = 0.032; FEV_1% pred and PEF % pred, p = 0.025) only in men, suggesting more severe COVID-19 disease and/or premorbid comorbidity in men.

4. Discussion

This observational study explored contributing factors to exercise intolerance in symptomatic patients with a mean of 6 months post-acute COVID-19 infection. We found a circulatory limitation (mean HRR <15 beats/min)(TS/ACCP,. 2003) in the VO_2 peak > 84% predicted group. We also found mean O_2 pulse peak % predicted (of 79 ± 12.9) was reduced in our sample (n = 59). O_2 pulse reflects the "amount of O_2 extracted per heartbeat".[15,p. 212; 10] O_2 pulse is equal to the product of stroke volume and the arterial-to-mixed venous O_2 content difference [C(a–v)O_2] (ATS/ACCP, 2003). We hypothesize that this impaired circulation and O_2 extraction, and low O_2 pulse (and likely lactic acid accumulation) contributed to early mental and peripheral muscle fatigue and early exercise termination. Impaired energy metabolism and mitochondrial bioenergetics as a mechanism of impaired exercise tolerance in long COVID is novel and similar to ME/CFS (Guntur et al., 2022). Our finding of CI – an indication of impaired autonomic function – may further explain persisting symptoms of long COVID, such as dyspnea and PEM; (Davenport et al., 2019) consistent with another long COVID-19 study (Balady et al., 2010; Jimeno-Almazán et al., 2021).

In our cohort, heart rate (HR) reserve was significantly higher in the reduced exercise capacity subgroup (those with VO_2 peak ≤84% predicted), possibly also indicating deconditioning. These participants demonstrated less energy expenditure (METs), shorter test duration, and higher heart rate reserve (1 −(peak heart rate/(220 −age))× 100; Table 1.

Mean VE reserve (VEmax /MVV) × 100) was 10.5 (4−26) for patients with VO_2 peak ≤ 84% predicted (in maximal CPET, Table 2), possibly also contributing to exercise intolerance and lower RER. A VE reserve of ≥ 15% of ventilatory capacity is considered normal (ATS/ACCP, 2003) Almost a third of subjects showed breathing inefficiency, defined as high (≥34) V_E/Vco_2 slope (Balady et al., 2010). Therefore, a ventilatory limitation may be a contributing factor to exercise intolerance in long COVID.

While a gold standard for defining maximal effort does not exist, a majority (57.6%) of subjects did not meet normative criteria for a maximal test, i.e., RER_{peak} (>1.05) supporting suboptimal effort. Our findings highlight exertional limitation and a high prevalence of early exercise termination in patients with long COVID-19. Consistent with our hypotheses, exertional limitation may be associated with autonomic dysfunction (CI, reduced peak systolic pressure, and breathing inefficiency) in adults with long COVID. Suboptimal effort (submaximal tests) was supported by another long COVID study (Motiejunaite et al., 2020).

A single administration of CPET may overestimate the exercise tolerance of patients with long COVID-19 because patients with PEM may not be able to reproduce exercise performance 24 h later (Nelson et al., 2019). We therefore recommend a more comprehensive evaluation of post-exercise recovery with 2-day CPET.

4.1. Limitations

A limitation of our study is that we did not collect data on comorbid medical conditions or quantify symptoms. However, all participants were symptomatic at the time of CPET testing. Timing of CPET varied widely for days post-positive COVID-19 test. Diffusing lung capacity for carbon monoxide (DLCO) data was not measured as a contributing factor in exercise intolerance. Impaired DLCO can persist in adults with long COVID and is associated with symptoms of exertional dyspnea. (Fortini et al., 2022) The heterogeneity of the sample (with the inclusion of both patients post-ICU with mechanical ventilation and those after only mild COVID-19 infection) limited the interpretation of our findings and our ability to characterize patients' ventilatory capacity. We also did not repeat CPET within 24 h to assess PEM and determine subjects' ability to reproduce VO_2 peak.

5. Conclusions

Impaired oxygen extraction, stroke volume (O_2 pulse), and CI were associated with long COVID. Impairments of O_2 uptake, delivery, and ventilation may contribute to persisting symptoms of long COVID-19, especially fatigue, post-exertional malaise, and dyspnea. Our study may help to advance understanding of biomarkers in long COVID and assist with the development of effective treatments. Considering *exercise as medicine*, (Oliveira and Hood, 2019) by improving oxygen metabolism and mitochondrial bioenergetics, tailored sub-symptom, low-intensity aerobic exercise may provide the right stimulus to help to treat long COVID (Guntur et al., 2022; Sorriento et al., 2021; Heo et al., 2023). Exercise improves nitric oxide, a potent vasodilator with anti-coagulant, antiviral, and antioxidant effects (Ricciardolo et al., 2020; Maiorana et al., 2003).

Supplier

R Core Team, 2022; The R Foundation.

Ethics approval

This study was approved by New York University's Institutional Review Board (i20–00909).

Study design

A. Norweg, L. Yao, T. Tarpey; data analyses: L. Yao and T. Tarpey; interpretation of the results: A. Norweg, S. Barbuto, A. Nordvig, E. Collins, and J. Leddy; manuscript writing: A. Norweg, S. Barbuto, A. Nordvig, E. Collins, J. Leddy, L. Yao, T. Tarpey, J. Whiteson, G. Sweeney, and F. Haas.

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Conflict of interest statement

Authors have no conflicts of interest to report.

Data Availability

The authors do not have permission to share data.

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