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Short communication

Cardiorespiratory physiology, exertional symptoms, and psychological burden in post-COVID-19 fatigue

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ABSTRACT

Fatigue is a common, debilitating, and poorly understood symptom post-COVID-19. We sought to better characterize differences in those with and without post-COVID-19 fatigue using cardiopulmonary exercise testing. Despite elevated dyspnoea intensity ratings, VO_2peak (ml/kg/min) was the only significant difference in the physiological responses to exercise (19.9 ± 7.1 fatigue *vs.* 24.4 ± 6.7 ml/kg/min non-fatigue, $p = 0.04$). Consistent with previous findings, we also observed a higher psychological burden in those with fatigue in the context of similar resting cardiopulmonary function. Our findings suggest that lower cardiorespiratory fitness and/or psychological factors may contribute to post-COVID-19 fatigue symptomology. Further research is needed for rehabilitation and symptom management following SARS-CoV-2 infection.

1. Introduction

Fatigue is the most common persistent symptom in COVID-19 survivors, with approximately 48% reporting fatigue > 12 weeks from diagnosis (Iqbal et al., 2021). Importantly, post-COVID-19 fatigue is not limited to those recovering from severe infection (Townsend et al., 2020) and its physiological basis is poorly understood. Cardiopulmonary exercise testing (CPET) is widely used to assess the physiological responses to exercise across multiple organ systems, and subsequently identify contributors to otherwise unexplained symptoms and/or exercise-related intolerance (American Thoracic Society and American College of Chest Physicians, 2003). While several studies have used CPET to investigate persistent symptoms and functional abnormalities post-COVID-19, a direct comparison of CPET outcomes between survivors with *vs.* without persistent fatigue has not been made. Accordingly, we sought to use CPET to better characterize differences in those with and without post-COVID-19 fatigue. In this exploratory study, we hypothesized that CPET in combination with symptom ratings throughout exercise would identify unique physiological and perceptual differences between COVID-19 survivors with and without persistent fatigue.

2. Methods

Individuals ≥ 18 years with SARS-CoV-2 infection by RT-PCR were prospectively recruited. Hospitalized individuals were invited to participate 3-months post-discharge and non-hospitalized individuals 3-months after their last positive SARS-CoV-2 test. The study received institutional ethical approval and participants provided written informed consent.

Participants rated their fatigue *before* and *during* infection from 0 to 4

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Table 1
Participant characteristics and exercise responses.

Variable	Fatigue	Non-Fatigue	p-value
n (%)	34 (69)	15 (31)	
Age, years	50 (38–58)	45 (31–59)	0.56
Male, n(%)	17 (50)	9 (60)	0.55
BMI, kg/m^2	30 ± 7	26 ± 5	0.06
Underweight, n(%)	0 (0)	0 (0)	
Normal weight, n(%)	9 (26)	7 (47)	
Overweight, n(%)	11 (32)	5 (33)	
Obese, n(%)	14 (41)	3 (20)	
Underweight, n(%)	0 (0)	0 (0)	
Fatigue pre-COVID-19, 0–4 scale	0.8 ± 0.8	0.3 ± 1.0	0.08
Fatigue during COVID-19, 0–4 scale	2.9 ± 0.9	2.4 ± 1.5	0.14
Fatigue post-COVID-19, 0–5 scale	1.7 ± 0.9	0.0 ± 0.0	< 0.001
Hospitalized, n (%)	13 (38)	4 (27)	0.53
Smoking history			
Current or former smoker, %	12 (35)	2 (13)	0.17
Pack years	4 ± 9	3 ± 9	0.59
Pulmonary function			
FEV$_1$, %predicted	95 ± 15	96 ± 8	0.77
FVC, %predicted	99 ± 16	100 ± 11	0.87
FEV$_1$/FVC	0.77 ± 0.06	0.78 ± 0.05	0.75
TLC, %predicted	90 ± 16	91 ± 13	0.84
RV, %predicted	77 ± 16	74 ± 17	0.59
DL$_{CO}$, %predicted	86 ± 15	97 ± 33	0.55
Cardiac function			
LVEF, %	64 ± 12	62 ± 5	0.93
Self-reported questionnaires			
HADS, total score	14.3 ± 8.1	7.8 ± 7.9	0.01
HADS, anxiety score	8.7 ± 4.7	5.8 ± 5.3	0.06
HADS, depression score	5.6 ± 4.2	2.0 ± 3.2	0.01
IES-R, total	26.5 ± 22.8	8.3 ± 17.0	0.01
IES-R, intrusion	10.1 ± 9.5	3.7 ± 7.6	0.03
IES-R, avoidance	9.7 ± 7.6	2.3 ± 4.0	0.001
IES-R, hyperarousal	6.7 ± 6.8	2.4 ± 6.1	0.049
PSS, score	17.5 ± 7.9	13.2 ± 9.6	0.16
D-12, total	7.2 ± 7.9	3.0 ± 9.4	0.11
D-12, physical	5.3 ± 5.3	2.0 ± 5.7	0.06
D-12, affective	1.9 ± 2.7	1.0 ± 3.9	0.34
mMRC, total	1.1 ± 1.0	0.3 ± 0.8	0.01
Peak incremental exercise			
$\dot{V}O_2$, l/min	1.70 ± 0.63	1.95 ± 0.76	0.23
$\dot{V}O_2$, ml/kg/min	19.9 ± 7.1	24.4 ± 6.7	0.04
METs, kcal/kg/hour	5.7 ± 2.0	7.0 ± 1.9	0.04
METs$_{adjusted}$, kcal/kg/hour	6.4 ± 2.0	7.6 ± 2.1	0.07
$\dot{V}O_2$, ml/ideal body mass (kg)/min	24.9 ± 7.2	27.3 ± 8.1	0.31
$\dot{V}O_2$, ml/height (cm)/min	9.9 ± 3.3	11.1 ± 3.9	0.25
$\dot{V}O_2$, %predicted	74 ± 20	81 ± 17	0.28
Work rate, watts	145 ± 57	172 ± 67	0.15
Heart rate, beats/min	153 ± 24	158 ± 31	0.50
Heart rate, %predicted	94 ± 12	94 ± 11	0.82
Chronotopic incompetence, n(%)	9 (26)	4 (27)	
$\dot{V}_E$, l/min	69.6 ± 25.0	77.8 ± 27.6	0.31
$\dot{V}_E/\dot{V}CO_2$ nadir	30.6 ± 4.3	29.2 ± 4.6	0.30
$\dot{V}_E$/MVV$_{est}$, %	63 ± 14	64 ± 14	0.77
SpO$_2$, %	97 ± 2	97 ± 1	0.87
RER	1.24 ± 0.09	1.25 ± 0.09	0.78
Dyspnoea intensity, 0–10 scale	8 ± 2	6 ± 2	0.04
Dyspnoea unpleasantness, 0–10 scale	7 ± 3	5 ± 2	0.10
Leg discomfort, 0–10 scale	8 ± 2	7 ± 2	0.14
Reasons for stopping			
Breathing, n(%)	11 (32)	2 (13)	0.29
Legs, n(%)	13 (38)	8 (53)	0.36
Combination n(%)	10 (29)	5 (33)	1.00
Perceptual-physiological relationships			
Dyspnoea intensity-$\dot{V}_E$ slope, 0–10 scale/l/min	0.14 ± 0.10	0.08 ± 0.04	0.04
Dyspnoea unpleasantness-$\dot{V}_E$ slope, 0–10 scale/l/min	0.14 ± 0.11	0.08 ± 0.04	0.07
Leg discomfort-Work rate slope, 0–10 scale/watts	0.06 ± 0.04	0.04 ± 0.01	0.06

Values represent number (percent), median (Q1-Q3), or mean ± standard deviation.
BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DL$_{co}$, diffusing capacity of the lungs for carbon monoxide; LVEF, left ventricular ejection fraction; HADS, Hospital Anxiety and Depression Scale; IER-S, Impact of Event Scale-Revised; PSS, Perceived Stress Scale; D-12, Dyspnoea-12; mMRC, modified Medical Research Council Dyspnoea Scale; $\dot{V}O_2$, oxygen consumption; METs, metabolic equivalents of task; METs$_{adjusted}$, METs adjusted using a correction factor for overweight and obese individuals; Chronotropic incompetence, heart rate reserve < 80%; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; MVV$_{est}$, estimated maximal voluntary ventilation (FEV$_1$ x 35); SpO$_2$, peripheral oxygen saturation; RER, respiratory exchange ratio.

(0 = I did not have this symptom, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) and *after* infection from 0 to 5 (0 = I no longer have this symptom, 1 =much better, 2 = somewhat better, 3 = about the same, 4 = somewhat worse, 5 = much worse). Participants were stratified based on the *after* scores at the time of their study visit, defined by any persistent fatigue relative to the acute phase of infection: *Fatigue*: score > 0, *Non-fatigue*: score = 0.

Self-administered questionnaires assessed the psychological impact of SARS-CoV-2 and the presence and impact of persistent dyspnoea. Blood samples were collected for biomarker analysis. Participants underwent transthoracic echocardiography, pulmonary function testing, and a symptom limited incremental cycling (15-watts/min) cardiopulmonary exercise test (CPET). Participants rated the intensity and unpleasantness of dyspnoea and leg discomfort using a 0–10 category-ratio Borg scale throughout exercise, and reported their main reason(s) for stopping exercise.

Individuals with comorbidities that could impact pulmonary function and/or exercise tolerance [*e.g.*, asthma with obstruction and/or shortness of breath (n = 8), chronic obstructive pulmonary disease (n = 1), interstitial lung disease (n = 1), moderate aortic stenosis (n = 1), and lung cancer (n = 1)] were excluded from this retrospective analysis. Unpaired t-tests and Fisher's Exact tests were used for between-group comparisons at baseline and peak exercise, and repeated measures ANOVA for submaximal exercise responses. Statistical significance was set at $p < 0.05$.

3. Results

Ninety-one individuals were screened from June-October 2020, 63 enrolled, and 49 met our inclusion criteria (34 fatigue, 15 non-fatigue; Table 1). There were no differences in fatigue scores before or during infection. A similar proportion of each group were hospitalized. Groups had similar age, sex, smoking history, pulmonary function, and left ventricular ejection fraction. Although average body mass index (BMI) was not statistically different ($p = 0.06$), there was a greater proportion of obese individuals in the fatigue group. There were no differences in erythrocyte sedimentation rate, N-terminal pro-B-type natriuretic peptide, C-reactive protein, D-dimer, or Vitamin D ($p > 0.05$).

Participants with fatigue had higher Hospital Anxiety and Depression Scale (HADS) total and depression scores. HADS anxiety scores were not different; however, average scores in the fatigue group rated positive for anxiety (score > 7). Impact of Event Scale-Revised total and domain scores were higher in the fatigue group. Perceived Stress Scale scores were not different; however, average scores suggest moderate stress (score ≥ 14) in those with fatigue *vs.* low stress (score ≤ 13)

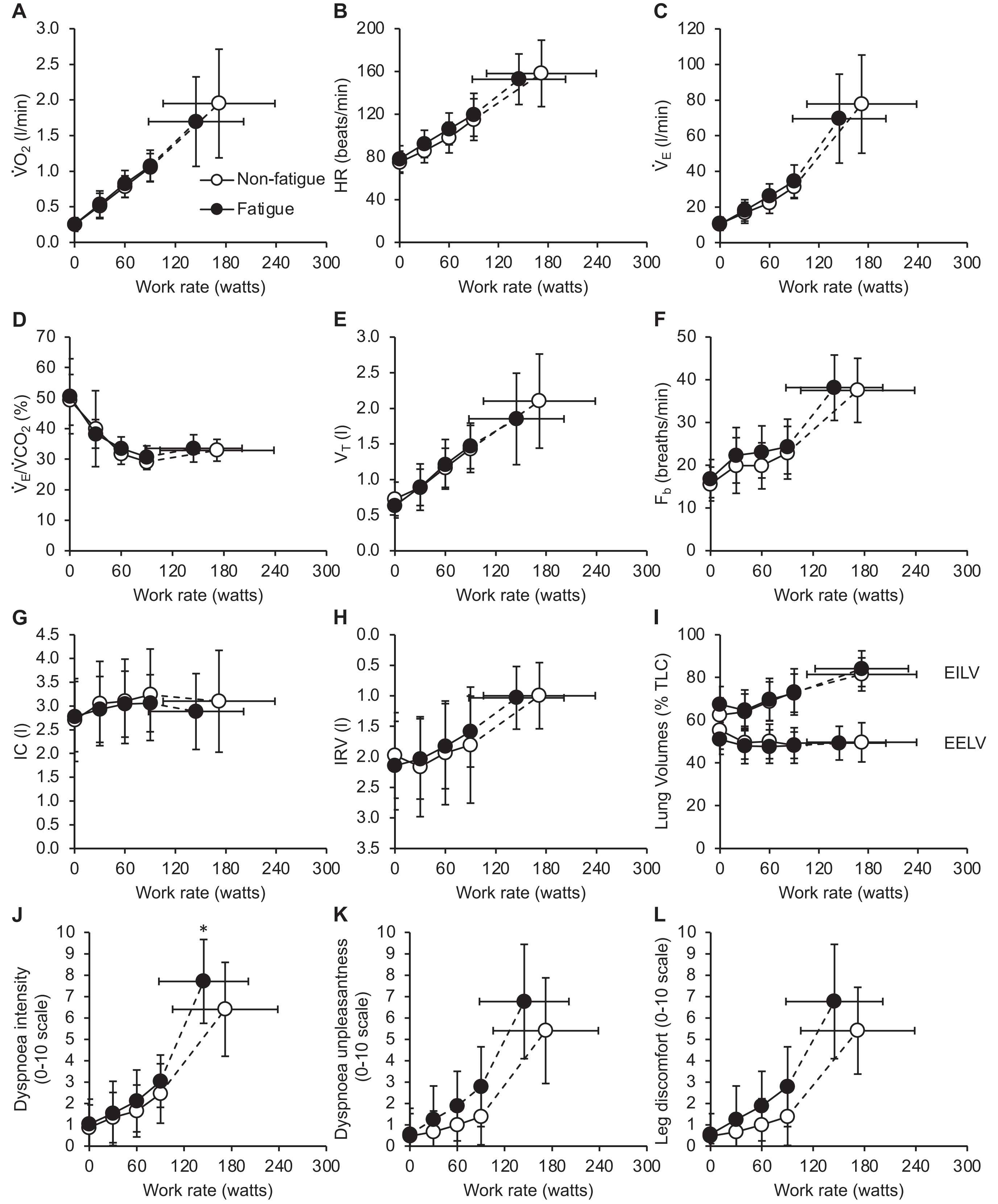

Fig. 1. Physiological and perceptual responses to exercise. Values are mean ± SD. Dashed lines connect the highest submaximal work rate achieved by all participants to the peak exercise data point. $\dot{V}O_2$, oxygen consumption; HR, heart rate; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; V_T, tidal volume; F_b, breathing frequency; IC, inspiratory capacity; IRV, inspiratory reserve volume; TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; * , $p < 0.05$ compared to non-fatigue group.

without. Modified Medical Research Council dyspnoea scores were higher in participants with fatigue.

Cardiopulmonary exercise responses were not different when expressed as absolute values or %predicted (Table 1, Fig. 1), except peak oxygen consumption ($\dot{V}O_2$) expressed in ml/kg/min, which was lower in the fatigue group. The gas exchange threshold ($n = 43$) occurred at a similar $\dot{V}O_2$ (l/min, $p = 0.44$; and %peak, $p = 0.76$) between groups. Peak metabolic equivalents of task (METs) were lower in the fatigue group, but not when adjusted for BMI (Wilms et al., 2014). Both groups achieved a respiratory exchange ratio > 1.15 and peak heart rate 94% predicted, which in the context of similar leg discomfort ratings and reasons for stopping exercise, suggests that groups were well matched for effort during the CPET.

There was no main effect of fatigue on the perceptual responses to exercise for a given work rate (Fig. 1) although peak dyspnoea intensity ratings as well as dyspnoea intensity-ventilation and -$\dot{V}O_2$ slopes were higher in the fatigue group. Dyspnoea unpleasantness and leg discomfort -work rate slopes between groups did not reach statistical significance (Table 1). There were no differences in reasons for stopping exercise.

4. Discussion

This is the first study to comprehensively assess the relationship between post-COVID-19 fatigue and cardiopulmonary function using CPET. There were no significant between-group differences in the physiological responses to exercise with the exception of $\dot{V}O_2$peak (ml/kg/min) despite significantly elevated dyspnoea intensity ratings during exercise. We also observed higher psychological burden in individuals with post-COVID-19 fatigue, which may contribute to symptomology.

The lower $\dot{V}O_2$peak (ml/kg/min) in the fatigue group indicates a lower cardiorespiratory fitness relative to the non-fatigue group. However, the fatigue group had a greater proportion of obese individuals whose cardiorespiratory fitness could be underestimated when $\dot{V}O_2$ is normalized to total body mass (Lorenzo and Babb, 2012). Alternatively, the groups were not different when $\dot{V}O_2$peak was normalized to ideal mass or height, or expressed as %predicted. When $\dot{V}O_2$peak is converted to METs adjusted for BMI (Wilms et al., 2014), average values were > 1-MET lower in the fatigue group, which is a clinically significant difference (Kodama et al., 2009) and suggests lower functional capacity relative to the non-fatigue group. Future work should include measurements of muscle strength, and also explore how those with post-COVID-19 fatigue respond to increasing their relative $\dot{V}O_2$ through exercise training and/or losing weight.

Participants with fatigue reported higher dyspnoea intensity ratings during CPET despite no differences in cardiovascular or ventilatory measures compared to those without fatigue. Additionally, those with fatigue reported higher anxiety, depression, distress, and functional disability attributable to dyspnoea. These observations are in the context of normal resting cardiopulmonary function and similar infection severity across groups, which is consistent with previous findings (Arnold et al., 2021; Stavem et al., 2021; Townsend et al., 2020). A higher psychological impact of COVID-19 could be associated with enhanced perception of symptoms, such as persistent fatigue, and the higher dyspnoea ratings for a given ventilation and $\dot{V}O_2$ we observed during exercise (Henningsen et al., 2003; Parshall et al., 2012). Accordingly, the roles of extra-cardiopulmonary factors, such as mental health, warrant further consideration.

We cannot discount the general impact of the pandemic on individuals, which is challenging to distinguish from the specific experience of having SARS-CoV-2 (Elia and Vallelonga, 2020; Stavem et al., 2021). Additionally, our study was limited by the use of a non-validated categorical assessment of fatigue. Our small sample size increased our probability of a type 2 error, with some outcome variables approaching but not reaching statistically significance. The lack of information related to fitness and other variables prior to and during SARS-CoV-2 infection also limits the generalizability of our findings.

In conclusion, lower cardiorespiratory fitness may contribute to post-COVID-19 fatigue. More research is needed to identify the pathophysiologic basis for the relatively lower $\dot{V}O_2$ in those with *vs.* without fatigue. Our study also highlights the psychological burden faced by individuals with post-COVID-19 fatigue, which may amplify symptom perception such as dyspnoea during exercise.

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CRediT authorship contribution statement

All authors played a role in the content and writing of the manuscript. Conceptualization: MRS, KMM, SJA, JAG; Design: JC, NV, VCM, KLL, SJA; Data collection: SJA, NV, JC; Data analysis: MRS, KMM, JHP, NV, AM, JAC, SJA, JAG.

Conflict of interest statements

None of the authors have any conflicts of interest that are directly relevant to the content of this article.

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