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Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors

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To the Editor:

There are increasing reports of persistent dyspnoea several months after the onset of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. In most cases, functional disability seems out of proportion compared to residual pulmonary function impairment [2]. To date, knowledge about the functional limitations following a SARS-CoV-2 infection remains limited.

The aim of our study was to evaluate pulmonary, cardiac and functional capacity of SARS-CoV-2 survivors by performing cardiopulmonary exercise testing (CPET). We performed a prospective single-centre study of 114 consecutive patients at 3±1 months after the initial diagnosis of SARS-CoV-2. All patients underwent pulmonary function tests, chest computed tomography (CT) and trans-thoracic echocardiogram, as well as symptom-limited CPET. Non-opposition was obtained for all patients, according to French law.

Incremental exercise testing was performed using cycle ergometer (Ergometrics 800S; GE). The peak oxygen uptake (peak V'_{O_2}), minute ventilation (V'_E) and heart rate were selected as the highest values obtained from any 30-s measurement period. The ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) slope was determined using linear regression analysis of V'_E and V'_{CO_2} obtained throughout the exercise period. The Wasserman equation was used to determine the normal predicted peak O_2 value [3], in accordance with recent recommendations [4].

The approach to interpretation of the main exercise limitation was multifactorial and in accordance with current guidelines [4, 5]. Cardiovascular limitation at exercise was defined when one or more of the following criteria were present: evidence of left ventricular systolic or diastolic dysfunction, reduced exercise capacity with low peak V'_{O_2} (<85% of predicted value), reduced oxygen pulse with a flattening curve during incremental exercise, chronotropic insufficiency or reduced peak circulatory power. Respiratory limitation was defined when one or more of the following criteria were present: 1) a significant reduction of pulmonary function at rest, *i.e.* forced expiratory volume in 1 s <70% of predicted and/or diffusing capacity of the lung for carbon monoxide (D_{LCO}) <70%; 2) breathing reserve (defined as peak V'_E/maximum voluntary ventilation <30%); or 3) hypoxaemia (peripheral capillary oxygen saturation (S_{pO_2}) ⩽88%) during exercise. Peripheral limitation was defined as a reduced peak V'_{O_2} with a premature anaerobic threshold below 40% of predicted in the absence of pulmonary or cardiac limitation. Inadequate exercise hyperventilation was defined as V'_E/V'_{CO_2} slope >40, increased ventilatory equivalents for CO_2 and O_2, as well as higher V'_E at anaerobic threshold in the absence of clear pulmonary or cardiac limitation.

The baseline characteristics of enrolled patients are reported in table 1. The median (range) age was 57 (48–66) years and one third were women. 12% of patients had a chronic pulmonary disease, such as COPD or asthma. Most patients (91%) required in-hospital treatment at the onset of the SARS-CoV-2, with 18% of the patients having required mechanical ventilation.

At 3-month follow-up, half of all patients were still symptomatic, dyspnoea (40%) and fatigue (32%) being the most common symptoms. 40% of patients had altered diffusion capacity, which was mild or moderate in all cases (D_{LCO} >40% of predicted value [6]). Mild to moderate residual lung involvement on chest CT

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Inadequate exercise hyperventilation should not be overlooked while exploring the causes of exertional dyspnoea in SARS-CoV-2 survivors https://bit.ly/3AxOiDh

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TABLE 1 Characteristics of SARS-CoV-2 infected patients at 3-month follow-up and results of pulmonary function tests, echocardiography and cardiopulmonary exercise testing (CPET) according to diffusion capacity of the lung for carbon monoxide (D_{LCO})

	All patients (n=114)	D_{LCO} >75% (n=63)	D_{LCO} ⩽75% (n=48)	p-value
Age, years	57 (48–66)	55 (47–67)	59 (48–66)	0.509
Female sex	38 (33%)	25 (40%)	10 (21%)	0.073
BMI, kg·m^{-2}	27.8 (24.2–30.1)	26.2 (24.6–30.9)	27.3 (24.2–30.6)	0.853
Comorbidities				
Hypertension	49 (43%)	27 (43%)	23 (48%)	0.529
Obesity (BMI >30 kg·m^{-2})	34 (30%)	20 (32%)	14 (29%)	1
Diabetes	25 (22%)	13 (21%)	13 (27%)	0.234
COPD/asthma	14 (12%)	4 (6%)	10 (21%)	0.049
Sleep apnoea	11 (10%)	5 (8%)	5 (10%)	0.682
Coronary artery disease	6 (5%)	3 (5%)	3 (6%)	1
Smoking status				0.102
Never	80 (70%)	49 (78%)	29 (60%)	
Former	31 (27%)	12 (19%)	18 (38%)	
Active	3 (3%)	2 (3%)	1 (2%)	
Initial COVID-19 management				
Conventional hospitalisation	104 (91%)	59 (87%)	45 (96%)	0.115
Severe form (requiring >6 L of O_2)	56 (49%)	26 (41%)	31 (66%)	0.071
ICU stay	25 (22%)	9 (14%)	17 (35%)	0.017
Endotracheal intubation with mechanical ventilation	21 (18%)	8 (13%)	13 (27%)	0.162
Hospital length of stay, days	10 (6–18)	9 (5–14)	12 (8–24)	0.019
Administration of high-dose steroids	54 (47%)	26 (41%)	28 (58%)	0.112
Degree of initial lung involvement				0.183
<25%	28 (36%)	17 (38%)	11 (31%)	
25–50%	36 (45%)	23 (52%)	13 (36%)	
50–75%	14 (18%)	3 (6%)	11 (31%)	
⩾75%	3 (3%)	2 (4%)	1 (2%)	
Persistent symptoms at 3 months follow-up				
Any persistent symptom	58 (51%)	34 (51%)	24 (51%)	0.23
Dyspnoea	45 (40%)	21 (33%)	23 (48%)	0.147
Fatigue	36 (32%)	17 (27%)	19 (40%)	0.259
Cough	16 (14%)	6 (9%)	10 (21%)	0.095
Chest pain	7 (6%)	7 (12)	0 (0%)	0.045
Pulmonary function tests				
VC % pred	90 (78–105)	94 (83–106)	81 (72–102)	0.004
FEV_1 % pred	93 (81–102)	97 (84–108)	83 (72–96)	<0.001
FEV_1/VC	0.81 (0.74–0.86)	0.81 (0.78–0.86)	0.81 (0.72–0.86)	0.128
TLC % pred	92 (77–105)	96 (85–108)	82 (73–97)	<0.001
D_{LCO} % pred	79 (65–90)	88 (82–97)	64 (55–70)	<0.001
K_{CO} % pred	92 (82–106)	102 (90–115)	84 (74–93)	<0.001
Degree of residual lung involvement on CT				0.018
Absent	40 (35%)	28 (47%)	11 (25%)	
<10%	40 (35%)	23 (39%)	16 (36%)	
10–25%	20 (18%)	6 (11%)	14 (32%)	
25–50%	5 (4%)	2 (3%)	3 (7%)	
Echocardiography				
Left ventricular ejection fraction, %	65 (60–68)	64 (61–68)	65 (56–71)	0.78
Left ventricular global longitudinal strain	18 (16–20)	19 (17–20)	17 (14–19)	0.017
Systolic pulmonary artery pressure, mmHg	27 (23–30)	27 (23–30)	27 (24–30)	0.896
Cardiopulmonary exercise testing				
Time from hospital discharge to CPET, days	90 (71–106)	90 (76–109)	87 (69–100)	0.089
Load reached, W	112 (73–144)	124 (97–149)	98 (83–136)	0.021
% of target heart rate	86 (80–95)	90 (82–98)	82 (72–91)	0.003
V'_{O_2}/W slope	9.34 (8.00–10.41)	9.34 (8.16–10.47)	9.30 (7.91–10.04)	0.373
Peak respiratory exchange ratio	1.19 (1.15–1.26)	1.18 (1.13–1.26)	1.20 (1.16–1.27)	0.174
Respiratory rate at peak exercise	37 (32–43)	37 (32–44)	37 (33–43)	0.891
Breathing reserve, %	43 (29–54)	38 (28–50)	47 (39–58)	0.008
V'_{O_2} at anaerobic threshold, mL·kg^{-1}·min^{-1}	10.3 (8.8–12.3)	10.9 (9.1–12.8)	9.8 (8.6–11.6)	0.075
V'_{O_2} at anaerobic threshold, % pred	43 (34–51)	45 (38–53)	39 (33–49)	0.014

Continued

TABLE 1 Continued

	All patients (n=114)	D_{LCO} >75% (n=63)	D_{LCO} ⩽75% (n=48)	p-value
Patients with predicted V'_{O_2} at anaerobic threshold <40%	49 (43%)	21 (33%)	28 (58%)	0.009
V'_{O_2} peak, mL·kg^{-1}·min^{-1}	17.9 (14.7–20.6)	19.0 (16.0–23.4)	16.2 (13.8–18.9)	0.002
V'_{O_2} peak, % pred	71 (60–85)	79 (64–87)	62 (55–76)	<0.001
Patients with predicted V'_{O_2} <85%	85 (75%)	43 (68%)	41 (85%)	0.034
Peak circulatory power	3112 (2268–3726)	3245 (2455–3861)	2771 (1994–3459)	0.018
Peak oxygen pulse, mL per beat	10.4 (8.1–12.4)	10.6 (8.4–12.5)	9.7 (7.6–12.2)	0.506
% of theoretical peak oxygen pulse	79 (66–93)	81 (70–93)	78 (64–87)	0.12
Δ oxygen pulse between rest and peak exercise, mL per beat	5.5 (4.1–7.7)	5.7 (4.2–7.9)	5.4 (3.9–7.4)	0.286
V'_E at anaerobic threshold, L·min^{-1}	27 (20–36)	28 (20–38)	28 (23–33)	0.964
V'_E at peak exercise, L·min^{-1}	61 (45–77)	67 (44–79)	56 (45–71)	0.184
V'_E/MVV at anaerobic threshold	0.28 (0.22–0.38)	0.27 (0.22–0.33)	0.30 (0.23–0.44)	0.167
V'_E/MVV at peak exercise	0.64 (0.52–0.78)	0.64 (0.54–0.76)	0.64 (0.51–0.77)	0.458
V'_E/V'_{CO_2} ratio at anaerobic threshold	30 (27–33)	30 (27–32)	31 (26–34)	0.178
V'_E/V'_{CO_2} ratio at peak exercise	36 (32–39)	35 (32–37)	37 (35–43)	0.021
V'_E/V'_{CO_2} slope	33 (30–38)	32 (30–36)	34 (30–40)	0.105
Elevated V'_E/V'_{CO_2} slope >35	37 (32%)	17 (27%)	19 (40%)	0.177
Presence of inappropriate hyperventilation	27 (24%)	11 (18%)	15 (31%)	0.141
Limitation at exercise				0.051
No limitation	40 (35%)	29 (46%)	10 (21%)	
Muscular deconditioning	51 (45%)	22 (35%)	28 (58%)	
Cardiovascular	0	0	0	
Pulmonary	1 (1%)	0	1 (2%)	
Exercise hyperventilation	19 (16%)	9 (14%)	8 (19%)	
Lack of motivation	3 (3%)	2 (3%)	1 (2%)	

Values are presented as median (interquartile range) for quantitative variables and as n (%) for qualitative variables. Comparisons between groups were performed with unpaired t-tests for normally distributed continuous variables and Mann–Whitney U-tests for non-normally distributed continuous variables. Chi-squared test of independence was used to test the distribution categorical variables. D_{LCO} measurements were available in 111 patients. BMI: body mass index; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ICU: intensive care unit; VC: vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; K_{CO}: carbon monoxide transfer coefficient; CT: computed tomography; V'_{O_2}: oxygen uptake; V'_E/V'_{CO_2}: ventilatory equivalent for carbon dioxide; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; MVV: maximal voluntary ventilation.

was found in 65% of patients. Trans-thoracic echocardiogram showed a normal left ventricular ejection fraction in the majority of the patients as well as a preserved global longitudinal strain. Pulmonary hypertension (systolic pulmonary artery pressure (sPAP) >40 mmHg) was detected in one patient.

During CPET, 75% of patients had exercise impairment with peak V'_{O_2} values <85% of predicted. The median (range) peak V'_{O_2} was 17.9 (14.7–20.6) mL·kg^{-1}·min^{-1}. Peripheral deconditioning was the main limiting factor in 43% of patients. 24% of patients had an elevated V'_E/V'_{CO_2} ratio at peak exercise (>40) and 32% had an elevated V'_E/V'_{CO_2} slope (>35). Exercise hyperventilation was the main limitation in 16% of patients. After adjustment for covariates, age (β=0.4, p=0.002), intensive care stay (β=−10.27, p=0.017), mechanical ventilation (β=−12.63, p=0.004) and length of hospital stay (β=−0.24, p=0.009) were independently associated with % predicted peak V'_{O_2}.

Patients who had altered diffusion capacity (D_{LCO} ⩽75%) reached a lower maximal load and had lower peak V'_{O_2} values at anaerobic threshold as well as at peak exercise. However, the prevalence of hyperventilation was similar in both groups. Interestingly, patients with reduced D_{LCO} did not report more persistent dyspnoea.

The prevalence of exercise limitation in our cohort was much higher than in a study by Rinaldo *et al.* [7]. In accordance with a previous report [7], reduced exercise capacity in our cohort was mostly due to peripheral deconditioning. However, our study also found an elevated V'_E/V'_{CO_2} slope in one third of the study participants, suggesting a high incidence of inadequate exercise hyperventilation. Our findings are supported by two previous studies [8, 9] which reported persistent ventilatory inefficiency in smaller cohorts of SARS-CoV-2 survivors who underwent CPET. Increased V'_E/V'_{CO_2} slope and reduced diffusion capacity might suggest pulmonary hypertension at exercise [10]. However, in our cohort only one patient had an elevated sPAP at rest. What is more, there was no statistically significant difference in V'_E/V'_{CO_2} according to D_{LCO} subgroups.

Exercise hyperventilation is a condition characterised by alveolar hyperventilation that is inappropriate considering metabolic needs and mechanical stress in the body [11]. The origin of this hyperventilation is unknown but may be related to an abnormality of central ventilatory control in the aftermath of pulmonary infection [12]. Increased output of the respiratory centre results in respiratory alkalosis [12], which in turn activates the autonomous nervous system, causing a variety of neurovegetative symptoms as well as arterial vasoconstriction and hypoperfusion [13]. The diagnosis of hyperventilation syndrome is usually established after exclusion of other cardiopulmonary diseases, such as heart failure, asthma or COPD. CPET is useful for the differential diagnosis of dyspnoea at exertion. Markers of hyperventilation include increased V'_E/V'_{CO_2} ratio and slope during exercise [14, 15], rapid increase in ventilatory equivalents for V'_{O_2} and V'_{CO_2}, abnormally high respiratory rate, and higher V'_E at anaerobic threshold [4]. Hyperventilation-related symptoms can range from dyspnoea, palpitations and chest pain, to dizziness and fatigue, which have been reported by the so-called "Covid long-haulers" [1]. Identification of hyperventilation syndrome is important, because the variety of disabling symptoms might take SARS-CoV-2 survivors to a wide range of specialist consultations, numerous investigations and inappropriate treatment, whereas respiratory physiotherapy with an experienced therapist with a focus on patient education can help significantly. Spontaneous recovery is also possible.

Our study has several limitations. Firstly, several parameters that could be of interest, such as end-tidal carbon dioxide tension and individual S_{pO_2} data, were unavailable for statistical analysis. However, none of the patients desaturated at exercise. Moreover, the limitations of reference values for CPET must be taken into account, as % of predicted values are less accurate for obese patients. However, the reference values that were used are in accordance with international guidelines. Another limitation of the study is the absence of arterial blood gas measurement, which could confirm the presence of respiratory alkalosis and thus further strengthen the diagnosis of hyperventilation syndrome. The noninvasive assessment of pulmonary gas exchange during exercise is less reliable and is known to produce higher values of ventilatory equivalents in patients without significant lung disease.

In conclusion, our study confirmed that peripheral deconditioning is the main mechanism of exercise intolerance in the aftermath of SARS-CoV-2. However, exercise hyperventilation should not be overlooked while exploring the causes of dyspnoea in SARS-CoV-2 survivors.

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