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

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



This article has an editorial commentary: https://doi.org/10.1183/13993003.01763-2021

Received: 4 June 2021
Accepted: 28 June 2021

*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

**Cite this article as:** Motiejunaite J, Balagny P, Arnoult F, *et al*. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. *Eur Respir J* 2021; 58: 2101578 [DOI: 10.1183/13993003.01578-2021].

**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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Author contributions: J. Motiejunaite, P. Balagny, F. Arnoult, L. Mangin, C. Bancal and J. Frija-Masson performed the cardiopulmonary function tests. J. Motiejunaite and P. Balagny performed a literature review and the statistical analysis. J. Motiejunaite, E. Vidal-Petiot and M. Flamant performed data collection and database management. J. Motiejunaite and J. Frija-Masson drafted the manuscript. P. Balagny, F. Arnoult, L. Mangin, C. Bancal, E. Vidal-Petiot, M. Flamant, G. Jondeau, A. Cohen-Solal and M-P. d'Ortho contributed significantly to manuscript correction and finalisation. All authors contributed to the article and approved the submitted version.

Conflict of interest: E. Vidal-Petiot reports personal fees and non-financial support from Servier, outside the submitted work. A. Cohen-Solal has received grants or honoraria from Novartis, Servier, Daiichi Sankyo, Vifor, Menarini and Cardiorentis, outside of the submitted work. J. Frija-Masson reports non-financial support from Vitalaire, Boehringer Ingelheim, Oxyvie and LVL Medical, outside the submitted work. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References


1 Carfi A, Bernabei R, Landi F, *et al.* Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603–605.

2 Frija-Masson J, Debray M-P, Boussouar S, *et al.* Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: the post Covid M3 study. *J Respir Med* 2021; 184: 106435.

3 Wasserman KHJ, Sue DY, Casaburi R, *et al.* Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. 3rd edition. Philadelphia, Lippincott, Williams & Wilkins, 1999.

4 American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.

5 Radtke T, Crook S, Kaltsakas G, *et al.* ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev* 2019; 28: 180101.

6 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.

7 Rinaldo RF, Mondoni M, Parazzini EM, *et al.* Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J* 2021; 58: 2100870.

8 Dorelli G, Braggio M, Gabbiani D, *et al.* Importance of cardiopulmonary exercise testing amongst subjects recovering from COVID-19. *Diagnostics* 2021; 11: 507.

9 Debeaumont D, Boujibar F, Ferrand-Devouge E, *et al.* Cardiopulmonary exercise testing to assess persistent symptoms at 6 months in people with COVID-19 who survived hospitalization - a pilot study. *Phys Ther* 2021; 101: pzab099.

10 Oliveira RKF, Waxman AB, Hoover PJ, *et al.* Pulmonary vascular and right ventricular burden during exercise in interstitial lung disease. *Chest* 2020; 158: 350–358.

11 Gardner WN. Hyperventilation: Diagnosis and Therapy. *In:* Beverly H, Timmons RL, eds. Behavioral and Psychological Approaches to Breathing Disorders. New York, Springer Science+Business Media, LLC, 1994, 99–111.

12 Jack S, Rossiter HB, Warburton CJ, *et al.* Behavioral influences and physiological indices of ventilatory control in subjects with idiopathic hyperventilation. *Behav Modif* 2003; 27: 637–652.

13 Motiejunaite J, Balagny P, Arnoult F, *et al.* Hyperventilation: a possible explanation for long-lasting exercise intolerance in mild COVID-19 survivors? *Front Physiol* 2020; 11: 614590.

14 Brat K, Stastna N, Merta Z, *et al.* Cardiopulmonary exercise testing for identification of patients with hyperventilation syndrome. *PLoS ONE* 2019; 14: e0215997.

15 Balady GJ, Arena R, Sietsema K, *et al.* Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; 122: 191–225.