Dora ANTUNES[1,2], Filipa MARQUES[1], Isabel SANTOS SILVA[1,2], Miguel BRANCO[1]
1. Departamento de Ginecologia, Obstetrícia, Reprodução e Neonatologia. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
2. Faculdade de Medicina. Universidade de Coimbra. Coimbra. Portugal.
Autor correspondente: Dora Antunes. dora.antunes9@gmail.com
Recebido/*Received*: 02/11/2022 - **Aceite/Accepted:** 15/02/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19283

Exercise Intolerance Following COVID-19: What Is the Role of Dysfunctional Breathing?

Intolerância ao Exercício Após COVID-19: Qual o Papel da Respiração Disfuncional?

Keywords: COVID-19; Exercise Test; Exercise Tolerance; Post-Acute COVID-19 Syndrome; Respiration
Palavras-chave: COVID-19; Respiração; Síndrome Pós_COVID-19 Agudo; Teste de Esforço; Tolerância ao Exercício

Dear Editor,

Cardiopulmonary exercise testing (CPET) has been used to explore persisting symptoms post-COVID-19. Different pathophysiological patterns have been reported[1-3]: oxygen transport/delivery problems, dysfunctional breathing (erratic or inappropriate ventilation during exercise),[4] ventilatory limitation, gas exchange abnormality, chronotropic insufficiency (reduced ability to increase heart rate during exercise) and dysautonomia. To explain these findings, a number of mechanistic explanations have been proposed,[1,2] namely deconditioning, endothelial injury, enhanced chemoreflex sensitivity, respiratory centre dysfunction and mitochondrial dysregulation.

We analysed our case series from Glasgow (Gartnavel General Hospital and Glasgow Royal Infirmary), Scotland, of 46 adult incremental symptom-limited CPETs (the standard protocol in the unit) performed because of breathlessness post-COVID-19 that was not fully explained by pulmonary function tests, chest imaging or echocardiogram. The data in this study are anonymised and retrospectively collected from tests performed as part of the routine clinical care of patients. Consequently, ethics committee approval was not sought for this analysis.

The median (IQR) duration from COVID diagnosis to CPET was 14 (10) months. The mean (SD) age was 51.9 (12.8) years, 63% were women, mean (SD) BMI was 31.1 (6.2) kg/m^2 and 30.4% (n = 14) were smokers/ex-smokers. As for comorbidities, 13 patients had asthma, one had COPD, six had systemic hypertension, four had mild anaemia, three had type 2 diabetes, one had ischemic heart disease and seven had been prescribed heart rate-control medication. Twelve patients were hospitalized with one being admitted to the high-dependence or intensive care unit. Six patients had pulmonary embolism and three had a diagnosis of chronic thromboembolic pulmonary disease. The mean (SD) forced expiratory volume in 1 second (FEV_1) was 101% (17) and transfer factor for carbon monoxide (TLCO) was 82% (19), of the predicted value. Lung imaging was abnormal in five [minor non-specific reticular changes or ground glass (n = 3); expiratory air trapping (n = 1); and hemidiaphragm elevation (n = 1)] and the echocardiogram was abnormal in three out of 25 patients tested (mildly dilated right ventricle, mild left ventricular systolic dysfunction and bicuspid aortic valve).

Only 27 subjects (59%) performed a maximal test. The remaining patients stopped before clear physiological limitation. The mean (SD) peak oxygen uptake (VO_2) was 20.7 (6.7) mL/kg/min and 88.2% (20.1) of predicted, with 14 patients (30.4%) having a peak VO_2 below the lower limit of normal (LLN) and 80% showing functional limitation with VO_2 < 25 mL/kg/min. The commonest abnormalities seen were dysfunctional breathing/acute hyperventilation (54%), gas exchange abnormalities (52%; with dysfunctional breathing in 72% of these cases) and oxygen transport/delivery problems typically of mild degree and consistent with deconditioning (35%). Evidence of dysfunctional breathing was seen in 64% of those with a peak VO_2 < LLN. Dysfunctional breathing was identified subjectively from an abnormality in the biomechanical pattern of breathing in response of exercise during the test. The commonest abnormality was an abrupt rise in the respiratory exchange ratio (RER, the ratio between the metabolic production of carbon dioxide and the uptake of oxygen) (> 1.0) and ventilatory equivalents in the early part of the test which then fell again as the test proceeded. This was usually combined with an irregular pattern of tidal volume and respiratory rate when plotted against ventilation. There were no cases of ventilatory limitation and there was one case of postural tachycardia syndrome (which has also been reported[5] with other viruses).

Other than dysfunctional breathing, we did not find a COVID-19 specific CPET pattern of exercise intolerance that could not be explained by other conditions. In our view and as previously reported,[2-4] breathing dysregulation may represent a possible pathophysiological explanation for much of the physical limitation post-COVID-19.

ACKNOWLEDGMENTS

We acknowledge the respiratory physiology staff at

Gartnavel General Hospital and Glasgow Royal Infirmary who supervised the performance of the cardiopulmonary exercise tests.

AUTHOR CONTRIBUTIONS

CF: Conception of the original idea, data collection, literature search, statistical analysis, writing of the manuscript.

MJ: Conception of the original idea, data collection, critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Naeije R, Caravita S. Phenotyping long COVID. Eur Respir J. 2021;58:2101763.
2. Motiejunaite J, Balagny P, Arnoult F, Mangin L, Bancal C, d'Ortho M, et al. Hyperventilation: a possible explanation for long-lasting exercise intolerance in mild COVID-19 survivors? Front Physiol. 2021;11:614590.
3. van Voorthuizen EL, van Helvoort HA, Peters JB, van den Heuvel MM, van den Borst B. Persistent exertional dyspnea and perceived exercise intolerance after mild COVID-19: a critical role for breathing dysregulation? Phys Ther. 2022;102:pzac105.
4. Frésard I, Genecand L, Altarelli M, Gex G, Vremaroiu P, Vremaroiu-Coman A, et al. Dysfunctional breathing diagnosed by cardiopulmonary exercise testing in 'long COVID' patients with persistent dyspnoea. BMJ Open Respir Res. 2022;9:e001126.
5. Freeman R, Wieling W, Axelrod FB, Benditt D, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21:69-72.

Carlos FIGUEIREDO✉[1], Martin JOHNSON[2]
1. Pneumology Department. Hospital de Santa Marta. Centro Hospitalar Universitário Lisboa Central. Lisbon. Portugal.
2. Scottish Pulmonary Vascular Unit. Queen Elizabeth University Hospital. Glasgow. United Kingdom.
✉ **Autor correspondente:** Carlos Figueiredo. figueiredocarloslopes@gmail.com
Recebido/*Received*: 22/12/2022 - **Aceite/*Accepted*:** 16/02/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19526